

Exhibit 24

Confidential Subject to Protective Order

1 UNITED STATES DISTRICT COURT
2 SOUTHERN DISTRICT OF NEW YORK
3
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5 -----X
6 IN RE: Acetaminophen -)
7 ASD-ADHD Products) Case No. 1:22-md-
8 Liability Litigation) 03043-DLC
9)
10 This Document Relates to:)
11)
12 All Cases)
13)
14 -----X

11 CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER
12 VIDEOTAPED DEPOSITION OF STAN G. LOUIE, PharmD
13 SANTA MONICA, CALIFORNIA
14 SATURDAY, AUGUST 7, 2023
15 9:02 A.M.
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22

23 Job No.: 341011
24 Pages: 1 - 325
25 Reported by: Leslie A. Todd, CSR No. 5129 and RPR

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1 Deposition of STAN G. LOUIE, PharmD, held at
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 15 Pursuant to notice, before Leslie Anne Todd,
 16 California Certified Shorthand Reporter in and for
 17 the State of California, who officiated in
 18 administering the oath to the witness.
 19
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 21
 22
 23
 24
 25

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1 **APPEARANCES (Continued):**
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<p>Page 11</p> <p>1 EXHIBITS CONTINUED</p> <p>2 (Attached to transcript)</p> <p>3 LOUIE DEPOSITION EXHIBITS PAGE</p> <p>4 No. 46 Article entitled: Perinatal</p> <p>5 exposure to paracetamol: Dose and</p> <p>6 sex-dependent effects in behavior</p> <p>7 and brain's oxidative stress</p> <p>8 markers in progeny, by Rigobello,</p> <p>9 et al. 255</p> <p>10 No. 47 Article entitled: Gestational</p> <p>11 exposure to paracetamol in rats</p> <p>12 induces neurofunctional alterations</p> <p>13 in the progeny, by Klein, et al. 259</p> <p>14 No. 48 Article entitled: Effects of</p> <p>15 paracetamol (acetaminophen) on</p> <p>16 gene expression and permeability</p> <p>17 properties of the rat placenta and</p> <p>18 fetal brain [version 2; peer review;</p> <p>19 2 approved], by Koehn, et al. 269</p> <p>20 No. 49 Article entitled: The impact of</p> <p>21 therapeutic doses of paracetamol</p> <p>22 on serum total antioxidant capacity,</p> <p>23 by Nuttall, et al. 285</p> <p>24</p> <p>25</p>	<p>Page 13</p> <p>1 A Stan G. Louie.</p> <p>2 Q And do you go by Dr. Louie? Should I</p> <p>3 use Mr. Louie? What would you prefer?</p> <p>4 A I like to be called Dr. Louie.</p> <p>5 Q Okay, Dr. Louie. I noted you came with</p> <p>6 some documents today. Do you mind if I take a</p> <p>7 quick look --</p> <p>8 A Sure.</p> <p>9 Q -- at the documents?</p> <p>10 And while I'm kind of looking through</p> <p>11 these, are these -- any of these documents new</p> <p>12 documents that aren't referenced in your report?</p> <p>13 A I do not believe so.</p> <p>14 Q Okay. And looking through them, it</p> <p>15 looks like documents referenced in your -- what is</p> <p>16 the -- this last one in the manilla folder that</p> <p>17 I'm looking at, Wisniewski 2019?</p> <p>18 MR. ADAMS: That's not yours. That's</p> <p>19 mine.</p> <p>20 MR. PADGETT: That's yours. Sorry.</p> <p>21 Okay.</p> <p>22 (Exhibit Nos. 21 and 22 were</p> <p>23 marked for identification.)</p> <p>24 BY MR. PADGETT:</p> <p>25 Q Those are all the documents you brought</p>

<p style="text-align: right;">Page 14</p> <p>1 with you today?</p> <p>2 A These are the documents I have.</p> <p>3 Q And they look like various studies that</p> <p>4 you discuss in your report, right?</p> <p>5 A Yes, that's correct.</p> <p>6 Q Have you conferred or met with</p> <p>7 plaintiffs' other disclosed experts in this case</p> <p>8 outside of the presence of counsel?</p> <p>9 A I'm not sure I understand what your</p> <p>10 question is.</p> <p>11 Q Have you been on any Zooms, have you had</p> <p>12 any meetings with plaintiffs' other disclosed</p> <p>13 experts, like Dr. Baccarelli and Dr. Pearson,</p> <p>14 outside the presence of plaintiffs' counsel?</p> <p>15 A Without the -- the attorneys?</p> <p>16 Q Correct.</p> <p>17 A I have not.</p> <p>18 Q Okay. Have you had any written</p> <p>19 communications with any of the plaintiffs' other</p> <p>20 disclosed experts while working on your reports,</p> <p>21 including your reply report, in which plaintiffs'</p> <p>22 counsel was not involved?</p> <p>23 A So you -- you had a number of questions.</p> <p>24 Can you break them down so that I can answer each</p> <p>25 and every one of them?</p>	<p style="text-align: right;">Page 16</p> <p>1 marked Exhibit 22, and I just want you to confirm</p> <p>2 for us that --</p> <p>3 MR. ADAMS: Just one second, Counsel.</p> <p>4 There are multiple copies in here, and -- in the</p> <p>5 folder. So --</p> <p>6 MR. PADGETT: Oh, I think --</p> <p>7 MS. KAPKE: One is for the court</p> <p>8 reporter and one is for him.</p> <p>9 MR. ADAMS: Just one second. You hold</p> <p>10 this.</p> <p>11 MR. PADGETT: Okay, I got that sorted</p> <p>12 out.</p> <p>13 BY MR. PADGETT:</p> <p>14 Q You also see before you Exhibit 22 has</p> <p>15 been marked. Can you confirm that that is your</p> <p>16 July 28, 2023 reply report in this case?</p> <p>17 A (Peruses document.) It appears so.</p> <p>18 Q Okay. And you might want to keep those</p> <p>19 handy or close by. We'll probably be referring to</p> <p>20 them quite a bit throughout the day.</p> <p>21 Dr. Louie, do you agree you're not an</p> <p>22 epidemiologist?</p> <p>23 A I'm not sure I understand the question.</p> <p>24 Q Do you consider yourself an</p> <p>25 epidemiologist?</p>
<p style="text-align: right;">Page 15</p> <p>1 Q Let me ask, have you -- have you had any</p> <p>2 communications with plaintiffs' counsel -- or with</p> <p>3 the other plaintiffs' experts, like Dr. Pearson,</p> <p>4 Dr. Baccarelli, Dr. Cabrera, written</p> <p>5 communications in which plaintiffs' counsel was</p> <p>6 not included in those communications?</p> <p>7 A So you're saying in the absence of an</p> <p>8 attorney, did I ever talk to them personally?</p> <p>9 Q Written communications.</p> <p>10 A No.</p> <p>11 Q I know your consulting agreement was</p> <p>12 dated March 14, 2023. When were you first</p> <p>13 contacted to work on this case?</p> <p>14 A Probably a week or two weeks before. I</p> <p>15 don't recollect exactly. Something like that.</p> <p>16 Q Okay. And I'm going to now -- it's</p> <p>17 already been marked for you. Do you see that</p> <p>18 before you is Exhibit No. --</p> <p>19 A Does it have to go to her?</p> <p>20 THE REPORTER: No.</p> <p>21 BY MR. PADGETT:</p> <p>22 Q -- Exhibit 21 is your amended report</p> <p>23 dated June 21, 2023, correct?</p> <p>24 A It -- it appears so.</p> <p>25 Q And the next one below that has been</p>	<p style="text-align: right;">Page 17</p> <p>1 A I'm not an epidemiologist, but I use</p> <p>2 epidemiology in my practice in the things that I</p> <p>3 do in terms of on project development and looking</p> <p>4 at population effects.</p> <p>5 Q Have you ever taught an epidemiology</p> <p>6 class?</p> <p>7 A I have not taught a class in</p> <p>8 epidemiology.</p> <p>9 Q Have you ever taken an epidemiology</p> <p>10 class, whether undergraduate or graduate level?</p> <p>11 A Well, epidemiology includes several</p> <p>12 things. I've taken -- I've taken a number of</p> <p>13 classes in biostatistics. I've taken -- which are</p> <p>14 the fundamental issues of -- I've taught in some</p> <p>15 of it how to consider in looking at medical</p> <p>16 evaluations and things like that. I teach my</p> <p>17 students biostats and how to analyze data.</p> <p>18 Q How to analyze data, but have you ever</p> <p>19 taken an -- a class that is designated</p> <p>20 Epidemiology 101, for example?</p> <p>21 MR. ADAMS: Object to form.</p> <p>22 THE WITNESS: I don't think there's such</p> <p>23 a class like that. We don't call it that.</p> <p>24 BY MR. PADGETT:</p> <p>25 Q Oh.</p>

<p style="text-align: right;">Page 18</p> <p>1 A It's normally like biostats, which is in</p> <p>2 preventive medicine is called PML 101. So you may</p> <p>3 not have the name, but it has all the elements</p> <p>4 because those are part of fundamental learning for</p> <p>5 scientists.</p> <p>6 Q Have you ever taken a class in</p> <p>7 undergraduate or graduate school in which the</p> <p>8 focus was on the study of cohorts of people and</p> <p>9 the effects of different types of risk factors?</p> <p>10 MR. ADAMS: Object to form.</p> <p>11 THE WITNESS: When we look at biostats,</p> <p>12 we look at that. That's one of the fundamental</p> <p>13 things that we do.</p> <p>14 We -- not only have taken a class, I</p> <p>15 practice in that, so therefore it's very important</p> <p>16 that I understand that.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q Have you ever served as a peer reviewer</p> <p>19 for any epidemiology study articles?</p> <p>20 A Can you repeat that again?</p> <p>21 Q Have you ever served as a peer reviewer</p> <p>22 for any epidemiology study articles that were</p> <p>23 proposed to be published?</p> <p>24 A I have not as a reviewer, but I've</p> <p>25 published in a number of these things.</p>	<p style="text-align: right;">Page 20</p> <p>1 A Mm-hmm.</p> <p>2 Q Have any of those studies involved ADHD?</p> <p>3 MR. ADAMS: Object to form.</p> <p>4 THE WITNESS: Not that I can recall.</p> <p>5 BY MR. PADGETT:</p> <p>6 Q And could we also have the agreement</p> <p>7 that we're going to use the abbreviation ADHD for</p> <p>8 attention-deficit/hyperactivity disorder?</p> <p>9 A Sure.</p> <p>10 Q And you mentioned that -- I think it's</p> <p>11 paragraph 68 of your report, your amended report,</p> <p>12 you describe your -- your experience with</p> <p>13 reviewing and evaluating epidemiology --</p> <p>14 epidemiological evidence in your work.</p> <p>15 Can you describe your experience in --</p> <p>16 in that regard?</p> <p>17 A There's -- there's a number of these</p> <p>18 things, so I need you to be more focused.</p> <p>19 Q What types of conditions, diseases, if</p> <p>20 any, have you studied or have you reviewed and</p> <p>21 evaluated with regard to epidemiological evidence</p> <p>22 in your work?</p> <p>23 MR. ADAMS: Object to form.</p> <p>24 THE WITNESS: Can you rephrase it a</p> <p>25 little bit better for me?</p>
<p style="text-align: right;">Page 19</p> <p>1 Q Did -- and you say you've published in a</p> <p>2 number of things. Did any of -- and these are</p> <p>3 human focused studies that you just referred to;</p> <p>4 is that correct?</p> <p>5 A Absolutely.</p> <p>6 Q Did any of them involve autism spectrum</p> <p>7 disorder?</p> <p>8 MR. ADAMS: Object to form.</p> <p>9 THE WITNESS: Not that I can recollect.</p> <p>10 BY MR. PADGETT:</p> <p>11 Q Did any of them involve -- and can we --</p> <p>12 can we get the agreement that we'll use ASD as our</p> <p>13 abbreviation for autism spectrum disorder?</p> <p>14 A Sure.</p> <p>15 Q Okay. And have you ever published an</p> <p>16 article or been a coauthor or author on an article</p> <p>17 involving human studies or a human study involving</p> <p>18 attention-deficit/hyperactive -- activity</p> <p>19 disorder?</p> <p>20 MR. ADAMS: Object to form.</p> <p>21 THE WITNESS: Can you repeat that again?</p> <p>22 BY MR. PADGETT:</p> <p>23 Q You referenced earlier that you have</p> <p>24 published or been a coauthor or an author on</p> <p>25 studies involving humans -- human studies, right?</p>	<p style="text-align: right;">Page 21</p> <p>1 BY MR. PADGETT:</p> <p>2 Q Let me ask it this way: Other than your</p> <p>3 work in this litigation, have you ever reviewed</p> <p>4 and evaluated epidemiological evidence, as you</p> <p>5 state in paragraph 68 of your report, studies</p> <p>6 involving ASD or ADHD?</p> <p>7 A I have not done with ASD-ADHD, but I</p> <p>8 have done it for a number of diseases. Like, for</p> <p>9 example, children and -- and the effects of aging</p> <p>10 on drug metabolism. I have done it for patients</p> <p>11 with HIV, and the way they change, the way they</p> <p>12 respond to various drugs.</p> <p>13 So there's a number of cases, and that's</p> <p>14 why it's hard to answer the question because you</p> <p>15 frame it into a very small box.</p> <p>16 Q Okay. I understand that.</p> <p>17 You testified that you have not reviewed</p> <p>18 or evaluated epidemiological studies as a part of</p> <p>19 your work involving -- with regard to ASD or ADHD.</p> <p>20 Have you done any reviewing or</p> <p>21 evaluating epidemiology studies as a part of your</p> <p>22 work with regard to studies on any</p> <p>23 neurodevelopmental diseases?</p> <p>24 MR. ADAMS: Object to form.</p> <p>25 THE WITNESS: I -- I'm doing that right</p>

<p style="text-align: right;">Page 22</p> <p>1 now.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q As part of this litigation?</p> <p>4 A No.</p> <p>5 Q Oh, what are you working on right now</p> <p>6 involving neurodevelopmental diseases?</p> <p>7 A I'm working on Alzheimer's and dietary</p> <p>8 effects an Alzheimer's.</p> <p>9 Q Anything else?</p> <p>10 A We're probably moving on to Parkinson's</p> <p>11 disease.</p> <p>12 Q Let me -- let me back up. Do you</p> <p>13 consider Alzheimer's a neurodevelopmental disease?</p> <p>14 A It's a neurodegenerative disease, but if</p> <p>15 you go all the way down to it, you could actually</p> <p>16 call it a neuroinflammatory disease.</p> <p>17 Q Okay. It's not a disease looking at in</p> <p>18 utero development leading to Alzheimer's, right?</p> <p>19 A No, it isn't.</p> <p>20 Q And I think you started to say that</p> <p>21 you've looked at Parkinson's disease; is that</p> <p>22 right?</p> <p>23 MR. ADAMS: Object to form.</p> <p>24 THE WITNESS: I'm looking at some of the</p> <p>25 effects of aging and the relationship to the</p>	<p style="text-align: right;">Page 24</p> <p>1 that exists in the epidemiological materials.</p> <p>2 Did I read that right?</p> <p>3 A I'm trying to get to it.</p> <p>4 Is it on line 8? Is that correct?</p> <p>5 Q Excuse me?</p> <p>6 A Is it line 8 -- 33, line 8?</p> <p>7 Q Yes.</p> <p>8 A Yes, I did state that.</p> <p>9 Q Okay. But by that sentence, do you mean</p> <p>10 that your focus is on dose-response issues in</p> <p>11 epidemiology studies?</p> <p>12 A It can include that, but it can also</p> <p>13 expand to other aspects. As you say, cohorts. It</p> <p>14 could talk about the sub-patient populations, the</p> <p>15 at-risk populations. And so, yes, it's a</p> <p>16 dosage -- focused on dosage. Look at an exposure</p> <p>17 is what -- is what I normally do.</p> <p>18 Q And if you turn to paragraph 15 of your</p> <p>19 report, you state there that you've been asked in</p> <p>20 this case to determine the, quote, dose/duration,</p> <p>21 end quote, at which prenatal exposure to</p> <p>22 acetaminophen increases the risk of developing ASD</p> <p>23 and ADHD.</p> <p>24 Is that right?</p> <p>25 A Yeah, using the publicly available</p>
<p style="text-align: right;">Page 23</p> <p>1 development of Parkinson's.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q Would you agree that examining</p> <p>4 Parkinson's disease is not the study of a</p> <p>5 neurodevelopmental disease?</p> <p>6 A I'm not sure I can agree with that. A</p> <p>7 lot of the molecular changes are similar.</p> <p>8 Q It does not involve -- would you agree</p> <p>9 that Parkinson's disease does not involve -- what</p> <p>10 you're doing does not involve looking at in utero</p> <p>11 development as it relates to future development of</p> <p>12 Parkinson's disease?</p> <p>13 A In the aspect of in utero, I agree with</p> <p>14 you there.</p> <p>15 Q Okay. Look at page -- or paragraph 33</p> <p>16 of your report.</p> <p>17 You state that -- there that --</p> <p>18 A Oh, could you wait until I get there?</p> <p>19 Q Sorry.</p> <p>20 A What is it again?</p> <p>21 Q Paragraph 33.</p> <p>22 You state there, quote: To be clear, I</p> <p>23 examined epidemiological data from the perspective</p> <p>24 of a pharmacologist; for example, by using</p> <p>25 dosing/duration and other pharmacological data</p>	<p style="text-align: right;">Page 25</p> <p>1 evidence.</p> <p>2 Q Okay. You --</p> <p>3 A Yeah.</p> <p>4 Q You agree that that was a fair statement</p> <p>5 about paragraph 15?</p> <p>6 MR. ADAMS: Object to form.</p> <p>7 THE WITNESS: Can you repeat your</p> <p>8 question?</p> <p>9 BY MR. PADGETT:</p> <p>10 Q Strike that.</p> <p>11 I just want to break this down a little</p> <p>12 further. Does your use of, quote, dose/duration,</p> <p>13 end quote, encompass dose amounts, dose frequency</p> <p>14 and dose duration?</p> <p>15 A You should consider at least those,</p> <p>16 and -- and the route may -- may affect that, and</p> <p>17 when you use it.</p> <p>18 Q So by "dose/duration," you mean at least</p> <p>19 looking at dose amounts, dose frequency, dose</p> <p>20 duration, the route of the dose, and when the dose</p> <p>21 is taken. Right?</p> <p>22 A Correct.</p> <p>23 Q Okay. Do you mean anything else by,</p> <p>24 quote, dose/duration there?</p> <p>25 MR. ADAMS: Object to form.</p>

<p style="text-align: right;">Page 26</p> <p>1 THE WITNESS: No, I think we were pretty</p> <p>2 good with that.</p> <p>3 BY MR. PADGETT:</p> <p>4 Q You note that -- I note on your CV you</p> <p>5 have some mammalian and rodent studies on your</p> <p>6 publication list.</p> <p>7 Have you done any mammalian</p> <p>8 developmental neurotoxicology research</p> <p>9 specifically?</p> <p>10 A So we don't publish on those things. We</p> <p>11 do it for the FDA, because I develop drugs as part</p> <p>12 of my career.</p> <p>13 Q When you say "those things," my question</p> <p>14 was specific as to developmental neurotoxicology</p> <p>15 mammalian studies.</p> <p>16 A I do.</p> <p>17 Q Okay. Can you describe for me what</p> <p>18 types of development -- and recognizing they're</p> <p>19 not published and you do them for the FDA, what</p> <p>20 types of developmental neurotoxicology mammalian</p> <p>21 studies have you done?</p> <p>22 A So I've done it in mice; I've done it in</p> <p>23 rats. And what we do is we give a mice or a rat a</p> <p>24 dose, one dose versus -- it could be repeat doses</p> <p>25 which could be up to six months to -- to nine</p>	<p style="text-align: right;">Page 28</p> <p>1 in -- in humans.</p> <p>2 Q Have you done any nonhuman mammalian</p> <p>3 research studies on acetaminophen?</p> <p>4 A So we use acetaminophen as a tool to</p> <p>5 cause hepatotoxicities. That's a -- one of the</p> <p>6 drug-related models that people use. So I don't</p> <p>7 publish on it, but use it as a way to cause</p> <p>8 hepatotoxicity.</p> <p>9 Q And what is the purpose of using</p> <p>10 acetaminophen in these studies to cause</p> <p>11 hepatotoxicity?</p> <p>12 A One, you could see what your drug</p> <p>13 effects is in mitigating hepatotoxicity, assuming</p> <p>14 that the drug you're proposing it to mitigate</p> <p>15 hepatotoxicity.</p> <p>16 Q So as I understand it, these unpublished</p> <p>17 research -- mammalian research studies that you're</p> <p>18 talking about do not study specifically -- or were</p> <p>19 not intended to study acetaminophen, but another</p> <p>20 drug in which you use acetaminophen as part of</p> <p>21 evaluating hepatotoxicity?</p> <p>22 MR. ADAMS: Object to form.</p> <p>23 THE WITNESS: It uses acetaminophen to</p> <p>24 mimic the model of hepatotoxicity.</p> <p>25 BY MR. PADGETT:</p>
<p style="text-align: right;">Page 27</p> <p>1 months, and we look at the effects on the -- the</p> <p>2 pups and the fetus.</p> <p>3 Q And these are for various types of</p> <p>4 drugs -- proposed drugs?</p> <p>5 MR. ADAMS: Object to form.</p> <p>6 THE WITNESS: It is predominantly drugs.</p> <p>7 We want to look at safety of these compounds in</p> <p>8 the -- in fetuses.</p> <p>9 BY MR. PADGETT:</p> <p>10 Q Have you done any developmental neurotox</p> <p>11 studies on acetaminophen?</p> <p>12 A Not neurotoxicity.</p> <p>13 Q Have you done any studies on -- any type</p> <p>14 of mammalian research studies on acetaminophen?</p> <p>15 A I have.</p> <p>16 MR. ADAMS: Object to form.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q Okay. What -- what studies -- what</p> <p>19 mammalian research studies have you done on</p> <p>20 acetaminophen?</p> <p>21 A Assuming that humans are mammalian,</p> <p>22 which I do, I've done it in human studies.</p> <p>23 Q And those -- and that -- those studies</p> <p>24 weren't published; is that right?</p> <p>25 A No, those are just for safety evaluation</p>	<p style="text-align: right;">Page 29</p> <p>1 Q And which drugs have you looked at in</p> <p>2 which you've used acetaminophen to model</p> <p>3 hepatotoxicity, which compounds?</p> <p>4 A There's a compound called</p> <p>5 dihydromyricetin, and there's flavonoids that</p> <p>6 people are claiming that it's effective.</p> <p>7 Q Can you restate that last --</p> <p>8 A Flavonoids. F-L-A-V-O-N-O-I-D.</p> <p>9 Q What type of drugs are flavonoids and</p> <p>10 dihy- --</p> <p>11 A Dihydromyricetin.</p> <p>12 Q Can you describe those drugs, please.</p> <p>13 A They're -- they're flavonoids.</p> <p>14 Q They're not drugs. They're substances</p> <p>15 used for flavoring?</p> <p>16 A They're compounds they call flavonoids</p> <p>17 because they're antioxidants. Okay. They're</p> <p>18 found in your tea; they're found in your beer.</p> <p>19 They're -- they're naturally derived compounds.</p> <p>20 And their ability to reduce oxidative stress, a</p> <p>21 lot of people are using that to -- to say that it</p> <p>22 protects the liver.</p> <p>23 Q And then you use the acetaminophen in</p> <p>24 these studies to trigger liver toxicity in</p> <p>25 examining these two compounds; is that right?</p>

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1 A Yeah, their -- their effects to prevent
2 hepatotoxicity.

3 Q And do you -- is the acetaminophen used
4 in these studies at levels intended to induce
5 liver toxicity in these animals?

6 MR. ADAMS: Object to form.

7 THE WITNESS: It -- it should.

8 BY MR. PADGETT:

9 Q At what levels do you dose these -- what
10 type of animals are we talking about? Mice, rats?

11 MR. ADAMS: Object to form.

12 THE WITNESS: It's mice, and I -- we've
13 done it in rats.

14 BY MR. PADGETT:

15 Q And at what levels do you dose the mice
16 at to induce liver toxicity?

17 A If I recollect, it's about 150 milligram
18 per kilogram. Rats, I think over 500 milligram
19 per kilogram.

20 Q And you use those doses because you're
21 confident that they have been shown to cause
22 hepatotoxicity in mice and rats, correct?

23 MR. ADAMS: Object to form.

24 THE WITNESS: I don't know if I'm
25 confident, but that's what the literature

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1 suggests.

2 BY MR. PADGETT:

3 Q Okay. You're getting paid to do these
4 studies, right?

5 MR. ADAMS: Object to form.

6 THE WITNESS: I'm sorry?

7 BY MR. PADGETT:

8 Q You're -- are you getting -- you're
9 getting paid to do these studies, whichever lab
10 that you're working with? We'll get to that.

11 A During my lab -- I'm not sure -- what do
12 you mean by get paid?

13 Q My question is that you said that you --
14 you hope that they will cause liver toxicity.

15 A Right.

16 Q I mean, how much do these studies cost
17 to do?

18 MR. ADAMS: Object to form.

19 THE WITNESS: I don't even look at those
20 numbers.

21 BY MR. PADGETT:

22 Q Okay.

23 A These are grants or they're contracts
24 from drug companies that ask us to do these
25 things.

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1 Q Do you do independent testing of these
2 dose amounts during these experiments to confirm
3 that they cause liver toxicity at these dose
4 levels you just referred to?

5 MR. ADAMS: Object to form.

6 THE WITNESS: I'm not sure what you mean
7 by that.

8 BY MR. PADGETT:

9 Q As a part of the -- these studies -- I
10 mean, you're studying these other two compounds
11 that you just discussed that I really can't
12 pronounce, and then you use acetaminophen as kind
13 of a mechanism to evaluate hepatotoxicity, right?

14 A Yes.

15 Q And as a part of these studies, do you
16 separately do -- evaluate acetaminophen for liver
17 toxicity without the dosing with those other
18 compounds?

19 A If I'm doing it correctly, I would do
20 a -- a control.

21 Q Right.

22 A And I would do a treatment, and I would
23 dose escalate. So therefore -- of the compound
24 that I'm interested in to look at what we call
25 protective effects and to show causation.

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1 Q Right. Is the control, is that dosed
2 with acetaminophen to evaluate kind of the
3 baseline for hepatotoxicity?

4 A Yes.

5 Q Okay. And have the controls shown
6 hepatotoxicity at 150 milligrams per kilograms in
7 mice and 500 milligrams per kilograms in rats?

8 A We do that -- if it's mice, it's 150.
9 In rats, it's 500. But you asked me if they all
10 get hepatotoxic, and the answer is no.

11 Q Sometimes they -- they don't at those
12 levels?

13 A Sometimes they don't.

14 Q But has -- but -- but they do show
15 hepatotoxicity at those levels, some of these mice
16 and some of these rats, right?

17 A In most incidents.

18 Q In most incidences. Okay.

19 Do you ever dose the rats at levels
20 below 500 milligrams per kilogram to induce liver
21 toxicity in these experiments?

22 A Not personally done these studies, but
23 I've evaluated a number of studies, and if you're
24 lower than the hepatotoxic doses, they're
25 considered subhepatic toxic doses.

<p style="text-align: right;">Page 34</p> <p>1 Q Have you see -- and you said you have</p> <p>2 reviewed studies involving rats and doses below</p> <p>3 500 milligrams per kilogram for hepatotoxicity?</p> <p>4 A Yes.</p> <p>5 Q And have you seen hepatotoxicity in rats</p> <p>6 dosed below 500 milligrams per kilogram in these</p> <p>7 studies?</p> <p>8 A Can you repeat that?</p> <p>9 Q Have you seen -- in these studies that</p> <p>10 you were just mentioning that you've looked at --</p> <p>11 A Uh-huh.</p> <p>12 Q -- you said you've never done studies</p> <p>13 yourself at below 500 milligrams per kilogram.</p> <p>14 Have you seen in these other studies</p> <p>15 using below 500 milligrams per kilogram</p> <p>16 hepatotoxicity in rats below 500 milligrams per</p> <p>17 kilogram?</p> <p>18 A Do -- can you rephrase that? Because</p> <p>19 the way you said it, it's actually very confusing.</p> <p>20 Q Have you seen studies or reviewed</p> <p>21 studies, as you just were talking about, in which</p> <p>22 dose levels below 500 milligrams per kilogram in</p> <p>23 rats have shown hepatotoxicity?</p> <p>24 A You're saying below 500 I see</p> <p>25 hepatotoxicity.</p>	<p style="text-align: right;">Page 36</p> <p>1 histopathological -- and what -- what was the</p> <p>2 other?</p> <p>3 A Biochemical.</p> <p>4 Q Biochemical. And these related to the</p> <p>5 liver effects?</p> <p>6 MR. ADAMS: Object to form.</p> <p>7 THE WITNESS: Usually people use them as</p> <p>8 what they call clinical markers.</p> <p>9 BY MR. PADGETT:</p> <p>10 Q You mentioned also human studies on</p> <p>11 acetaminophen. Are these human studies on</p> <p>12 acetaminophen or human studies involving the use</p> <p>13 of acetaminophen as part of the control?</p> <p>14 MR. ADAMS: Object to form.</p> <p>15 THE WITNESS: It's patients receiving</p> <p>16 acetaminophen.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q Okay. Can you just describe these</p> <p>19 studies that you're talking about for us.</p> <p>20 A Patients -- I'll be on the record like</p> <p>21 this: Elderly patients in nursing homes receiving</p> <p>22 analgesics, comparing acetaminophen versus</p> <p>23 non-acetaminophen.</p> <p>24 Q And what was the purpose of these</p> <p>25 studies?</p>
<p style="text-align: right;">Page 35</p> <p>1 Q In rats. That's the question.</p> <p>2 A I haven't seen the reports like that.</p> <p>3 Q Okay. Are you saying, though, that --</p> <p>4 is it -- are you aware of rats having</p> <p>5 hepatotoxicity at below 500 milligrams per</p> <p>6 kilogram doses?</p> <p>7 MR. ADAMS: Object to form.</p> <p>8 THE WITNESS: I'm not aware.</p> <p>9 BY MR. PADGETT:</p> <p>10 Q All right. I think you mentioned --</p> <p>11 what do you mean by subtoxic hepatotoxicity? Can</p> <p>12 you explain what you mean by that?</p> <p>13 A So 500 milligram is, quote/unquote,</p> <p>14 hepatotoxic. Anything below it is considered</p> <p>15 subhepatic toxic doses.</p> <p>16 Q Is there a difference between -- let me</p> <p>17 ask this: What exactly do you mean by</p> <p>18 "hepatotoxicity"?</p> <p>19 A The context is two things. When you</p> <p>20 evaluate it at the right time points that there is</p> <p>21 either histological or biochemical changes leading</p> <p>22 you to believe that there is hepatic toxic</p> <p>23 doses -- hepatotoxicity.</p> <p>24 Q And you're -- again, you are not aware</p> <p>25 of studies showing those types of</p>	<p style="text-align: right;">Page 37</p> <p>1 A The ability to resolve pain in these</p> <p>2 individuals.</p> <p>3 Q Were you looking at hepatotoxicity or</p> <p>4 any other type of toxicity in these studies?</p> <p>5 A We looked at safety bio -- biomarkers,</p> <p>6 which means we looked at -- I think we did monthly</p> <p>7 blood tests, which is -- has a -- has the blood</p> <p>8 test for the biochemical markers, and we didn't</p> <p>9 see -- we didn't detect a -- a rise.</p> <p>10 Q Okay. And were these doses for these</p> <p>11 elderly people at therapeutic doses of</p> <p>12 acetaminophen pursuant to product labeling?</p> <p>13 A Part of my -- my part of the study, I</p> <p>14 was blinded or masked on what they got.</p> <p>15 Q Did you see the end results of the</p> <p>16 study, though?</p> <p>17 A I did not.</p> <p>18 Q So you don't -- you noted earlier -- you</p> <p>19 just testified earlier, though, that there weren't</p> <p>20 any biomarkers of toxicity seen from -- in these</p> <p>21 weekly blood tests that you mentioned from the</p> <p>22 dosing with acetaminophen. Is that right?</p> <p>23 A It was not weekly. It was monthly.</p> <p>24 Q Monthly. Sorry.</p> <p>25 A Yeah. I didn't see any, and in the</p>

<p style="text-align: right;">Page 38</p> <p>1 safety reports, I didn't -- don't recollect.</p> <p>2 Q You don't recollect any or you -- seeing</p> <p>3 any?</p> <p>4 MR. ADAMS: Object to form.</p> <p>5 THE WITNESS: I don't recollect because</p> <p>6 there is a safety monitor who would tell me that</p> <p>7 there is.</p> <p>8 BY MR. PADGETT:</p> <p>9 Q Are any of these -- any of these human</p> <p>10 studies published?</p> <p>11 A I was not the lead author, so I don't</p> <p>12 know if they got completed or not.</p> <p>13 Q You're not a medical doctor, right?</p> <p>14 A I think I'm a pharmacologist.</p> <p>15 Q All right. Have you received training</p> <p>16 on how to diagnose ASD or ADHD?</p> <p>17 A That's not my training.</p> <p>18 Q I guess my question is, have you</p> <p>19 received any training, though, on how to diagnose</p> <p>20 ASD or ADHD?</p> <p>21 MR. ADAMS: Object to form.</p> <p>22 THE WITNESS: I have read in the DSM how</p> <p>23 to. It doesn't mean that I know how to do it.</p> <p>24 BY MR. PADGETT:</p> <p>25 Q Okay. You list on your CV a number of</p>	<p style="text-align: right;">Page 40</p> <p>1 A That's part of USC.</p> <p>2 Q Are you involved with any laboratories</p> <p>3 or do you have any laboratory positions</p> <p>4 independent of USC?</p> <p>5 A I'm not sure I understand what that</p> <p>6 means.</p> <p>7 Q Is all your employment with laboratories</p> <p>8 associated with University of Southern California?</p> <p>9 A And my CV tells you that I -- I'm also a</p> <p>10 founder of a couple of biotechs, and those -- each</p> <p>11 of those companies may have a laboratory in</p> <p>12 itself.</p> <p>13 Q Do you actively work in those</p> <p>14 laboratories for those biotech companies?</p> <p>15 MR. ADAMS: Object to form.</p> <p>16 THE WITNESS: I don't actively supervise</p> <p>17 them, but I -- I receive data from them.</p> <p>18 BY MR. PADGETT:</p> <p>19 Q And did you have to get approval to</p> <p>20 testify in this litigation from USC?</p> <p>21 A I did not.</p> <p>22 Q Do you routinely read the literature on</p> <p>23 ASD as part of your work outside of the work in</p> <p>24 this litigation?</p> <p>25 A I think most of my work that I do is</p>
<p style="text-align: right;">Page 39</p> <p>1 positions at USC and labs.</p> <p>2 Are the Ginsburg Institute,</p> <p>3 PharmacoAnalytical Library, and the Clinical</p> <p>4 Experimental therapeutic -- Therapeutics Lab</p> <p>5 positions that you mention on your CV part of USC?</p> <p>6 MR. ADAMS: Object to form.</p> <p>7 THE WITNESS: You mean the Ginsburg</p> <p>8 Institute of Biomedical Technology? Or</p> <p>9 therapeutics -- I'm sorry, therapeutics?</p> <p>10 BY MR. PADGETT:</p> <p>11 Q I read on your CV Ginsburg Institute of</p> <p>12 PharmacoAnalytical library -- laboratory, but --</p> <p>13 what -- the Ginsburg Institute, is that</p> <p>14 independent or part of USC?</p> <p>15 A That's part of USC.</p> <p>16 Q Okay.</p> <p>17 A The PharmacoAnalytical laboratory is my</p> <p>18 laboratory.</p> <p>19 Q Is that part of USC?</p> <p>20 A That's part of USC. And the Clinical</p> <p>21 Experimental Therapeutics is the PhD and the</p> <p>22 master's program that I -- that I'm in charge of</p> <p>23 which leads -- essentially teaches laboratory as</p> <p>24 well as pharmacologic -- pharmacology development.</p> <p>25 Q And that's -- is that part of USC?</p>	<p style="text-align: right;">Page 41</p> <p>1 drug related. If it's -- if there's a drug</p> <p>2 related issue, I will review it. I'm a pediatric</p> <p>3 pharmacologist, so I'm very in tune with that.</p> <p>4 Do I routinely review it? I think I</p> <p>5 would look at it if there is something that I am</p> <p>6 interested and I think that that's something that</p> <p>7 I should investigate.</p> <p>8 Q And would you characterize that as</p> <p>9 occasional versus routinely?</p> <p>10 MR. ADAMS: Object to form.</p> <p>11 THE WITNESS: I'm not sure what the</p> <p>12 difference is. If you give me context, that would</p> <p>13 help me.</p> <p>14 BY MR. PADGETT:</p> <p>15 Q Well, let me ask for ADHD, do you</p> <p>16 regularly read literature on ADHD as part of your</p> <p>17 work outside of your work in this litigation?</p> <p>18 MR. ADAMS: Object to form.</p> <p>19 THE WITNESS: I may not look at ADHD,</p> <p>20 but as you already know, that I'm involved in the</p> <p>21 neurological development. That's part of the</p> <p>22 things I do. I look at the landscape of potential</p> <p>23 drugs that I can develop and potential unmet</p> <p>24 medical need. Those are the things I work on.</p> <p>25 BY MR. PADGETT:</p>

<p style="text-align: right;">Page 42</p> <p>1 Q And when you say, As you know, I look at</p> <p>2 neurological, that's Alzheimer's and Parkinson's,</p> <p>3 right?</p> <p>4 A No, I work on other things as -- that</p> <p>5 are probably not as familiar to you, but, yeah, I</p> <p>6 work on like -- things like ALS, things that are</p> <p>7 probably a lot more -- we use the term "orphan,"</p> <p>8 rare. I like to work on rare diseases.</p> <p>9 Q Dr. Louie, is it your opinion that any</p> <p>10 compound that causes a statistically significant</p> <p>11 neurochemical change or changes in the developing</p> <p>12 brain leads to an increased risk of ASD?</p> <p>13 MR. ADAMS: Object to form.</p> <p>14 THE WITNESS: Can you repeat that?</p> <p>15 MR. PADGETT: Can you read it back?</p> <p>16 THE REPORTER: Sure.</p> <p>17 "Dr. Louie, is it your opinion that any</p> <p>18 compound that causes a statistically significant</p> <p>19 neurochemical change or changes in the developing</p> <p>20 brain leads to an increased risk of ASD?</p> <p>21 MR. ADAMS: Object to form.</p> <p>22 Are you asking for a different opinion</p> <p>23 than he's rendered in his report?</p> <p>24 BY MR. PADGETT:</p> <p>25 Q You can --</p>	<p style="text-align: right;">Page 44</p> <p>1 BY MR. PADGETT:</p> <p>2 Q What neurochemical changes have been</p> <p>3 accepted in the scientific community as mechanisms</p> <p>4 that lead to ASD?</p> <p>5 MR. ADAMS: Object to form.</p> <p>6 THE WITNESS: You're once again giving</p> <p>7 me no context as to what chemical.</p> <p>8 BY MR. PADGETT:</p> <p>9 Q Well, you talk about acetaminophen in</p> <p>10 your report, and primarily the NAPQI and GSH</p> <p>11 related mechanism as a -- agreed, you talk about</p> <p>12 that quite a bit in your report, right?</p> <p>13 A That's the focus of my report.</p> <p>14 Q My question is, taking a step back, what</p> <p>15 mechanisms have been identified in the scientific</p> <p>16 community as changes in the brain from a</p> <p>17 biochemical standpoint that lead to ASD?</p> <p>18 MR. ADAMS: Object to form.</p> <p>19 THE WITNESS: So that was not on my</p> <p>20 assignment, so I did not actually delve in deep</p> <p>21 into understanding the literature. So I couldn't</p> <p>22 answer you because I didn't -- I don't have enough</p> <p>23 knowledge.</p> <p>24 BY MR. PADGETT:</p> <p>25 Q Okay. And is the same response true for</p>
<p style="text-align: right;">Page 43</p> <p>1 A You're not being specific.</p> <p>2 So any chemical is -- I think this is</p> <p>3 why it's hard to answer it. If you're talking</p> <p>4 about acetaminophen, it's in my report.</p> <p>5 Q Okay.</p> <p>6 A But if you're talking about any</p> <p>7 chemical, you are so broad that any chemical</p> <p>8 changes -- you got to be a lot more focused in</p> <p>9 your context.</p> <p>10 Q Well, I guess that's part of why I'm</p> <p>11 asking the question.</p> <p>12 Not just limited to acetaminophen, what</p> <p>13 specific -- do you have an opinion outside this</p> <p>14 litigation on whether a statistically significant</p> <p>15 neurochemical change or changes in the developing</p> <p>16 brain from an exposure to a compound leads to an</p> <p>17 increased risk of ASD?</p> <p>18 MR. ADAMS: I'm going to object to form.</p> <p>19 Now, you've made it clear you're asking</p> <p>20 for an opinion that he hasn't offered in his</p> <p>21 report.</p> <p>22 So you can go ahead.</p> <p>23 THE WITNESS: Yeah, I was not assigned</p> <p>24 to offer an opinion. And I have not reviewed it,</p> <p>25 so I'm not comfortable in reviewing it.</p>	<p style="text-align: right;">Page 45</p> <p>1 what neurochemical changes have been accepted in</p> <p>2 the scientific community that lead -- in the brain</p> <p>3 that lead to ADHD?</p> <p>4 MR. ADAMS: Object to form to the extent</p> <p>5 that you're talking about something that is not in</p> <p>6 his report.</p> <p>7 MR. PADGETT: He's talking about ADHD</p> <p>8 and mechanisms in his report --</p> <p>9 MR. ADAMS: Right, and I'm making --</p> <p>10 MR. PADGETT: -- and ASD.</p> <p>11 MR. ADAMS: I want to make clear that</p> <p>12 you're asking him for mechanisms that are outside</p> <p>13 of the opinions he's rendered in his report.</p> <p>14 MR. PADGETT: His opinions are on ASD</p> <p>15 and ADHD and neurochemical changes and mechanisms.</p> <p>16 So I'm asking what -- similar to what he just</p> <p>17 responded, what --</p> <p>18 BY MR. PADGETT:</p> <p>19 Q Can you identify neurochemical changes</p> <p>20 that are mechanisms accepted in the scientific</p> <p>21 community that lead to ADHD?</p> <p>22 A So --</p> <p>23 MR. ADAMS: Object to form.</p> <p>24 Go ahead.</p> <p>25 THE WITNESS: Yeah, so I'm going to say</p>

<p style="text-align: right;">Page 46</p> <p>1 it again. That was not my assignment. I did not</p> <p>2 investigate it, so I'm not comfortable in</p> <p>3 rendering any type of opinion.</p> <p>4 BY MR. PADGETT:</p> <p>5 Q Okay. Let me ask you -- well, do you</p> <p>6 agree that the biological mechanisms underlying</p> <p>7 ASD are still unknown?</p> <p>8 MR. ADAMS: Object to form.</p> <p>9 THE WITNESS: You're asking me to render</p> <p>10 an opinion that I was not assigned to, and I have</p> <p>11 not investigated into it.</p> <p>12 BY MR. PADGETT:</p> <p>13 Q Okay. Is the same true -- same question</p> <p>14 with regard to ADHD, you do not -- you've not been</p> <p>15 asked to -- well, strike that.</p> <p>16 Do you agree that the biological</p> <p>17 mechanisms underlying ADHD are still unknown?</p> <p>18 MR. ADAMS: Object to form.</p> <p>19 THE WITNESS: Once again, I was not</p> <p>20 assigned to -- to evaluate that, so therefore I</p> <p>21 cannot render any type of opinion.</p> <p>22 BY MR. PADGETT:</p> <p>23 Q And when you say you cannot render any</p> <p>24 type of opinion, is that -- does that mean you do</p> <p>25 not know --</p>	<p style="text-align: right;">Page 48</p> <p>1 any other case involving acetaminophen exposure?</p> <p>2 A Not that -- not directly as a single</p> <p>3 compound.</p> <p>4 Q Have you -- have you ever been involved</p> <p>5 in any other case involving acetaminophen exposure</p> <p>6 in any way?</p> <p>7 MR. ADAMS: Object to form.</p> <p>8 THE WITNESS: So when you say "case,"</p> <p>9 you mean a --</p> <p>10 BY MR. PADGETT:</p> <p>11 Q Litigation.</p> <p>12 A Oh, litigation. Okay. Thank you for</p> <p>13 that clarification.</p> <p>14 I looked at acetaminophen toxicity in a</p> <p>15 human case because of a toxicity that occurred in</p> <p>16 the hospital. The patient was taking Percocet,</p> <p>17 which has acetaminophen in it.</p> <p>18 Q And what was the nature of that</p> <p>19 litigation?</p> <p>20 A Not a litigation. It was a -- remember,</p> <p>21 I told you --</p> <p>22 Q Yeah, I'm talking about litigation.</p> <p>23 A Okay. Then I have not.</p> <p>24 MR. PADGETT: Let's take a break.</p> <p>25 THE VIDEOGRAPHER: We are going off the</p>
<p style="text-align: right;">Page 47</p> <p>1 MR. ADAMS: Object to form.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q -- because you haven't looked into it,</p> <p>4 right?</p> <p>5 A I think I'm going to maintain the same</p> <p>6 answer. I did not review it. I'm not comfortable</p> <p>7 in telling you something that I have not reviewed</p> <p>8 the entire landscape.</p> <p>9 Q Okay. I noticed in the invoices that</p> <p>10 you produced that the last one was dated -- or</p> <p>11 that were produced on your behalf, the last one</p> <p>12 was dated June 27. How much more time have you</p> <p>13 spent working on this case since that June 27</p> <p>14 invoice?</p> <p>15 A I think I -- during that -- between that</p> <p>16 time to, I guess, a month later, I had to do the</p> <p>17 rebuttal. So I think it's safe to say if you add</p> <p>18 them all up together, there's a total of 140 hours</p> <p>19 at least.</p> <p>20 Q That's 140 hours since June 27?</p> <p>21 A No, from the beginning of March 14th.</p> <p>22 Q And how -- how many hours since June 27?</p> <p>23 A I don't -- I couldn't tell you. I would</p> <p>24 have to look at my calendar.</p> <p>25 Q Have you ever been involved in any --</p>	<p style="text-align: right;">Page 49</p> <p>1 video record at 9:52 a.m.</p> <p>2 (Recess.)</p> <p>3 THE VIDEOGRAPHER: We are going back on</p> <p>4 the video record at 10:04 a.m.</p> <p>5 BY MR. PADGETT:</p> <p>6 Q Back from a quick break, Dr. Louie.</p> <p>7 My large water bottle is now safely on</p> <p>8 the floor. Everybody's safe.</p> <p>9 I want to go back to a couple -- couple</p> <p>10 of issues.</p> <p>11 First of all, in response to my question</p> <p>12 about whether you could identify the mechanisms --</p> <p>13 the biochemical mechanism that leads to ASD, you</p> <p>14 indicated that you were not assigned to look at</p> <p>15 that for purposes of this case; is that right?</p> <p>16 MR. ADAMS: Object to form.</p> <p>17 THE WITNESS: I don't think that's --</p> <p>18 can you rephrase it?</p> <p>19 BY MR. PADGETT:</p> <p>20 Q Dr. Louie, do you know the mechanism,</p> <p>21 the biological -- biochemical mechanism -- strike</p> <p>22 that.</p> <p>23 Do you know the biochemical mechanism --</p> <p>24 mechanisms that lead to autism?</p> <p>25 MR. ADAMS: Object to form.</p>

<p style="text-align: right;">Page 50</p> <p>1 THE WITNESS: You're still being very</p> <p>2 broad. If you would focus it down to</p> <p>3 acetaminophen, I may be able to help you.</p> <p>4 BY MR. PADGETT:</p> <p>5 Q My question is, do you have an</p> <p>6 understanding of the biochemical mechanisms that</p> <p>7 lead to ASD?</p> <p>8 MR. ADAMS: Object to form. He's</p> <p>9 answered the question.</p> <p>10 You can answer it again.</p> <p>11 THE WITNESS: I believe if you focus it</p> <p>12 to a specific, it will be a lot easier to answer</p> <p>13 your question.</p> <p>14 BY MR. PADGETT:</p> <p>15 Q Well, that -- that's my point is do you</p> <p>16 have an understanding, regardless of compound, of</p> <p>17 the biological mechanisms that lead to autism</p> <p>18 spectrum disorder?</p> <p>19 MR. ADAMS: Object to form.</p> <p>20 THE WITNESS: I think in this context if</p> <p>21 you're talking about acetaminophen, I do have a --</p> <p>22 a molecular mechanism that is -- that is very</p> <p>23 reasonable to explain this.</p> <p>24 BY MR. PADGETT:</p> <p>25 Q We'll be getting to that.</p>	<p style="text-align: right;">Page 52</p> <p>1 on that.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q And therefore, you don't know what</p> <p>4 biomechanism -- biochemical changes have been</p> <p>5 shown to be mechanisms that lead to ASD, correct?</p> <p>6 A That's not how I answered your question.</p> <p>7 Q Okay. Well, answer my question, please.</p> <p>8 MR. ADAMS: Okay. Object to form. He</p> <p>9 is answering your question.</p> <p>10 So let's just ask another question, and</p> <p>11 then consider it and answer it.</p> <p>12 THE WITNESS: Yeah, so I --</p> <p>13 MR. ADAMS: No, no, no, wait for another</p> <p>14 question.</p> <p>15 THE WITNESS: Okay.</p> <p>16 MR. ADAMS: There's no question pending.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q There's really -- do you know a</p> <p>19 mechanism -- a biochemical mechanism that has been</p> <p>20 shown to lead to ASD?</p> <p>21 A As I stated to you, your question is way</p> <p>22 too broad, and without context, it's not fair.</p> <p>23 Q So you're refusing to answer.</p> <p>24 A No.</p> <p>25 MR. ADAMS: Object to form.</p>
<p style="text-align: right;">Page 51</p> <p>1 My question is, are -- is it -- did you</p> <p>2 look at the biomechanism -- the biochemical</p> <p>3 mechanisms broadly that have been shown to lead to</p> <p>4 ASD, if any?</p> <p>5 MR. ADAMS: Object to form.</p> <p>6 THE WITNESS: If I -- could you repeat</p> <p>7 that again?</p> <p>8 BY MR. PADGETT:</p> <p>9 Q Did you look at the biomechanisms --</p> <p>10 biochemical mechanisms, the changes in the brain</p> <p>11 that lead to ASD?</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 THE WITNESS: I looked at it in the</p> <p>14 context of acetaminophen.</p> <p>15 BY MR. PADGETT:</p> <p>16 Q Okay. Beyond acetaminophen, do you have</p> <p>17 an understanding or have you looked at the</p> <p>18 biochemical changes in the brain that are</p> <p>19 mechanisms that lead to ASD?</p> <p>20 A That was not on my assignment.</p> <p>21 Q And by saying, "That was not on my</p> <p>22 assignment," do you agree you don't know?</p> <p>23 MR. ADAMS: Object to form.</p> <p>24 THE WITNESS: I just told you that</p> <p>25 because it's not on my assignment, I did not focus</p>	<p style="text-align: right;">Page 53</p> <p>1 THE WITNESS: No, it's because there --</p> <p>2 each chemical is not the same. Each compound is</p> <p>3 not the same. So therefore, if you ask me</p> <p>4 acetaminophen, I can give you a better answer.</p> <p>5 BY MR. PADGETT:</p> <p>6 Q Outside of acetaminophen, can you</p> <p>7 describe a biochemical change in the brain</p> <p>8 resulting from exposure to a compound that has</p> <p>9 been shown to lead to ASD?</p> <p>10 MR. ADAMS: Object to form.</p> <p>11 THE WITNESS: That was not on my</p> <p>12 assignment.</p> <p>13 BY MR. PADGETT:</p> <p>14 Q And therefore, you don't know; is that</p> <p>15 correct?</p> <p>16 MR. ADAMS: Object to form.</p> <p>17 THE WITNESS: As I stated to you, if</p> <p>18 it's not in my assignment, I did not investigate,</p> <p>19 and if I didn't investigate enough, I can't give</p> <p>20 you -- render you an opinion.</p> <p>21 BY MR. PADGETT:</p> <p>22 Q Okay. Outside of your investigation, do</p> <p>23 you know of a mechanism -- for this case, do you</p> <p>24 know of a biochemical change in the brain that is</p> <p>25 a mechanism that leads to ASD?</p>

<p style="text-align: right;">Page 54</p> <p>1 MR. ADAMS: Object to form.</p> <p>2 THE WITNESS: I believe I actually</p> <p>3 answered your questions a number of times. So --</p> <p>4 so I told you, if you don't give me context, I</p> <p>5 can't give you --</p> <p>6 BY MR. PADGETT:</p> <p>7 Q Okay. Here's the context: Outside of</p> <p>8 the GSH --</p> <p>9 MR. ADAMS: Well, before we do that, can</p> <p>10 we -- can we let the witness answer the question</p> <p>11 before you cut him off?</p> <p>12 BY MR. PADGETT:</p> <p>13 Q Oh, I'm sorry, did I cut you off? Were</p> <p>14 you not done?</p> <p>15 A Yes.</p> <p>16 Q Go ahead.</p> <p>17 A Thank you.</p> <p>18 I think I stated to you that the</p> <p>19 chemical -- it depends on the chemical, elicits</p> <p>20 different activity. So until you give me context,</p> <p>21 a specific compound, I don't like to use</p> <p>22 generalizable because I couldn't give you a</p> <p>23 specific answer.</p> <p>24 Q Can you identify another compound that</p> <p>25 has been shown to cause exposure to which has been</p>	<p style="text-align: right;">Page 56</p> <p>1 a specific compound, it's really hard.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q I'm asking you for a specific compound.</p> <p>4 Do you know a compound that has been shown to lead</p> <p>5 to ASD?</p> <p>6 A Is this part of my --</p> <p>7 MR. ADAMS: One second. Object to form.</p> <p>8 Now you can go.</p> <p>9 THE WITNESS: Yeah. Is this my</p> <p>10 assignment here?</p> <p>11 MR. ADAMS: No need --</p> <p>12 MR. PADGETT: No.</p> <p>13 MR. ADAMS: One second. Counsel, give</p> <p>14 me a second.</p> <p>15 So we're going to do it this way:</p> <p>16 Question, answer. You don't need to ask him a</p> <p>17 question. Just listen to the question, consider</p> <p>18 it, answer it.</p> <p>19 BY MR. PADGETT:</p> <p>20 Q As you sit here today, regardless of</p> <p>21 whether you investigated it for this litigation,</p> <p>22 can you identify a compound, outside of</p> <p>23 acetaminophen as discussed in your report, that</p> <p>24 has been identified as a cause of ASD?</p> <p>25 A Can you repeat that?</p>
<p style="text-align: right;">Page 55</p> <p>1 shown to cause ASD?</p> <p>2 A Like I told you, since you didn't</p> <p>3 specify, I'm -- it's outside of my -- my</p> <p>4 assignment, and I will not comment on that because</p> <p>5 I have not investigated it.</p> <p>6 Q Have you investigated it outside of this</p> <p>7 litigation mechanisms -- biochemical changes that</p> <p>8 have been shown to cause ASD?</p> <p>9 A Once again, you are not giving me</p> <p>10 context. I cannot give you an answer.</p> <p>11 Q What context would help you provide an</p> <p>12 answer, Dr. Louie?</p> <p>13 A Give me a specific compound that you're</p> <p>14 referring to, and if I do know, I will tell you.</p> <p>15 But because you're so broad, it could be gasoline,</p> <p>16 it could be air pollution. I don't know the</p> <p>17 answer.</p> <p>18 Q Okay. Do you know the answer to the</p> <p>19 question of what -- other than your opinions here</p> <p>20 about acetaminophen, what other compounds have</p> <p>21 been shown to cause ASD?</p> <p>22 A So --</p> <p>23 MR. ADAMS: Object to form.</p> <p>24 THE WITNESS: So I think we're going in</p> <p>25 circles, but to answer your question, unless I get</p>	<p style="text-align: right;">Page 57</p> <p>1 THE REPORTER: "As you sit here today,</p> <p>2 regardless of whether you investigated it for this</p> <p>3 litigation, can you identify a compound, outside</p> <p>4 of acetaminophen as discussed in your report, that</p> <p>5 has been identified as a cause of ASD?"</p> <p>6 THE WITNESS: I have not.</p> <p>7 BY MR. PADGETT:</p> <p>8 Q So would you agree then that you do not</p> <p>9 know -- you have not identified a mechanism in</p> <p>10 terms of a biochemical change in the brain that</p> <p>11 has been shown to lead to ASD?</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 THE WITNESS: I do not agree with you,</p> <p>14 because what you said was -- you asked me for a</p> <p>15 compound, you asked me for a mechanism. Like I</p> <p>16 said, I don't know what you're asking for, so</p> <p>17 therefore, I can't give you an answer.</p> <p>18 But then you tell me do I agree that I</p> <p>19 do not understand a molecular mechanism. That's</p> <p>20 not how I understand your question.</p> <p>21 BY MR. PADGETT:</p> <p>22 Q There's a section in your report where</p> <p>23 you talk about your work on cancer drugs or</p> <p>24 cancer, and you suggest a -- I think inflammation.</p> <p>25 Are -- do you believe that inflammation</p>

<p style="text-align: right;">Page 58</p> <p>1 is a mechanism that causes ASD?</p> <p>2 A Can you refer me to my -- where in my --</p> <p>3 so I want to make sure I understand the context.</p> <p>4 Q You state in your report, paragraph 5,</p> <p>5 you name a bunch of infectious diseases, cancer,</p> <p>6 autoimmune diseases, and you state that they share</p> <p>7 a common underlying pharmacological, mechanistic</p> <p>8 and inflammatory aspects --</p> <p>9 THE REPORTER: Excuse me, Counsel.</p> <p>10 Could I get you to slow down?</p> <p>11 MR. PADGETT: Yes.</p> <p>12 THE REPORTER: "You state that they</p> <p>13 share"?</p> <p>14 BY MR. PADGETT:</p> <p>15 Q -- "share common underlying</p> <p>16 pharmacological, mechanistic and inflammatory</p> <p>17 aspects of neurodevelopmental disorders such as</p> <p>18 autism spectrum disorder and attention</p> <p>19 hyperactivity disorder, which are discussed in</p> <p>20 this report."</p> <p>21 Okay. I'm asking you what mechanisms in</p> <p>22 terms of biochemical changes in the brain have</p> <p>23 been shown in the scientific -- in the science --</p> <p>24 scientific studies to lead to autism. Can you</p> <p>25 identify those?</p>	<p style="text-align: right;">Page 60</p> <p>1 A I -- I'm not -- I cannot do that right</p> <p>2 now. Not on top of my head.</p> <p>3 Q And in turn, since you're asking for a</p> <p>4 specific compound, you cannot as you sit here</p> <p>5 today identify a biochemical change in the brain</p> <p>6 that leads to a mechanism that causes ADHD, right?</p> <p>7 MR. ADAMS: Object to form.</p> <p>8 THE WITNESS: You're concluding</p> <p>9 something that I just -- unless I have a compound</p> <p>10 and I understand where you're coming from, it's</p> <p>11 going to be hard for me to discuss the potential</p> <p>12 mechanisms.</p> <p>13 BY MR. PADGETT:</p> <p>14 Q But if you cannot identify a compound as</p> <p>15 you sit here today, you also cannot identify a</p> <p>16 biochemical change related to a compound that</p> <p>17 leads to ASD. Right?</p> <p>18 A If you know that there's a compound, you</p> <p>19 should suggest it. And so therefore because you</p> <p>20 don't suggest it, you're making me speculate, and</p> <p>21 I don't like to speculate.</p> <p>22 Q Are the biological mechanisms accepted</p> <p>23 in the scientific community as causes of ASD still</p> <p>24 unknown?</p> <p>25 MR. ADAMS: Object to form.</p>
<p style="text-align: right;">Page 59</p> <p>1 A So the question that -- let me sort of</p> <p>2 rephrase what -- not rephrase -- actually read off</p> <p>3 exactly what I wrote.</p> <p>4 "Since then my research has expanded to</p> <p>5 include drug development for inflammation and</p> <p>6 immune-mediated diseases, including infectious</p> <p>7 disease, cancer, autoimmune diseases, retinal</p> <p>8 disorders, and neurodegenerative disorders. These</p> <p>9 studies -- these diseases share common underlying</p> <p>10 pharmacological, mechanistic and inflammatory</p> <p>11 aspects with neurodevelopmental disorders such as</p> <p>12 ASD and ADHD, which are discussed in this report."</p> <p>13 Q Okay.</p> <p>14 A So I do discuss in this report that --</p> <p>15 the effect of interleukin-1 beta, and it was found</p> <p>16 specifically in the fetus of animals that were --</p> <p>17 that were given acetaminophen. And it was not in</p> <p>18 the mother but it was in the animals.</p> <p>19 Q Is it your opinion that changes in</p> <p>20 interleukin-2 in the fetus lead to ASD or ADHD?</p> <p>21 A That's not how I state it into the</p> <p>22 report. So if -- do you mind if I go to that part</p> <p>23 of the report?</p> <p>24 Q Can you identify a compound that has</p> <p>25 been shown to cause ADHD?</p>	<p style="text-align: right;">Page 61</p> <p>1 THE WITNESS: It depends who you talk</p> <p>2 to.</p> <p>3 BY MR. PADGETT:</p> <p>4 Q What do you mean by "it depends who you</p> <p>5 talk to"?</p> <p>6 A Some people who work on the mechanisms</p> <p>7 think that there is. There's some others who say</p> <p>8 that the evidence is not strong enough.</p> <p>9 Q Can you -- have you -- can you identify</p> <p>10 a biological mechanism underlying ASD that has</p> <p>11 been accepted in the scientific community?</p> <p>12 A I think in this report I discuss</p> <p>13 acetaminophen as one of them. So I think if you</p> <p>14 attempt that as the -- as a potential, or even</p> <p>15 better yet, a candidate for cause.</p> <p>16 So this is where I think you want to</p> <p>17 talk about the broad, but you have a compound</p> <p>18 right here that shows you a lot of -- you know,</p> <p>19 gives you the thought that this may cause it.</p> <p>20 Q Can you identify, other than the GSH and</p> <p>21 CYP2E1 mechanism that you discuss in your report,</p> <p>22 another biological change or mechanism that leads</p> <p>23 to ASD?</p> <p>24 A I'm trying to understand why I would go</p> <p>25 off on something that --</p>

<p style="text-align: right;">Page 62</p> <p>1 Q Well, either you can name another</p> <p>2 mechanism or you can't, or you're refusing to</p> <p>3 answer, Dr. Louie.</p> <p>4 MR. ADAMS: Object -- object to form.</p> <p>5 That is absolutely not what's happening here. I</p> <p>6 think he's trying to answer your question. He's</p> <p>7 telling you why he's got confusion with your</p> <p>8 question. Apparently you're not accepting that.</p> <p>9 So again, I want to tell you, Dr. Louie,</p> <p>10 no need to argue with him. Just -- just get the</p> <p>11 question, consider it, and then answer it.</p> <p>12 MR. PADGETT: Julien --</p> <p>13 MR. ADAMS: And it'll go much faster and</p> <p>14 further if you do this.</p> <p>15 MR. PADGETT: Object to form.</p> <p>16 MR. ADAMS: Well, I will, and I've been</p> <p>17 doing that, but now it's devolving into bickering,</p> <p>18 and I don't think that's necessary.</p> <p>19 MR. PADGETT: Please read the question</p> <p>20 back.</p> <p>21 THE REPORTER: "Well, either you can</p> <p>22 name another mechanism or you can't, or you're</p> <p>23 refusing to answer, Dr. Louie."</p> <p>24 MR. ADAMS: Object to form.</p> <p>25 I'm going to instruct him not to answer.</p>	<p style="text-align: right;">Page 64</p> <p>1 Q We'll get to the data.</p> <p>2 I think before we broke you were talking</p> <p>3 about a case, but it wasn't litigation that</p> <p>4 involved acetaminophen.</p> <p>5 Have you been involved in any litigation</p> <p>6 involving acetaminophen?</p> <p>7 A I have not.</p> <p>8 Q Have you ever been in any litigation</p> <p>9 involving ASD or ADHD?</p> <p>10 A I have not.</p> <p>11 Q You note in your report at page 10, if</p> <p>12 you want to look at it, that you reviewed</p> <p>13 Dr. Baccarelli's expert report, and I also noted</p> <p>14 that Dr. Baccarelli's and Dr. Brandon Pearson's</p> <p>15 reports are listed in your reliance materials.</p> <p>16 Why -- we've already discussed</p> <p>17 Dr. Baccarelli, but why did you review</p> <p>18 Dr. Pearson's report?</p> <p>19 A I think it was sent to me after I</p> <p>20 already wrote my report, and to be complete, they</p> <p>21 sent it to me. And although I didn't consider it,</p> <p>22 I have to put it here that I reviewed it.</p> <p>23 Q So you did not rely on anything in</p> <p>24 Dr. Pearson's report for your opinions in this</p> <p>25 case?</p>
<p style="text-align: right;">Page 63</p> <p>1 That is literally not a question that's</p> <p>2 appropriate. So just ask him a proper question.</p> <p>3 BY MR. PADGETT:</p> <p>4 Q Can you name a biological mechanism</p> <p>5 outside of what's in your report that has been</p> <p>6 identified as a scientifically accepted mechanism</p> <p>7 that leads to ASD?</p> <p>8 A I reviewed the data in relationship to</p> <p>9 acetaminophen that shows you that glutathione, the</p> <p>10 patient is a potential, if not a candidate for the</p> <p>11 cause.</p> <p>12 Q And so as you sit here today, you cannot</p> <p>13 name, other than what's in your report -- what's</p> <p>14 discussed in your report, a mechanism in terms of</p> <p>15 a biological change in the brain that leads to ASD</p> <p>16 or ADHD.</p> <p>17 MR. ADAMS: Object --</p> <p>18 BY MR. PADGETT:</p> <p>19 Q Is that correct?</p> <p>20 MR. ADAMS: Object to form.</p> <p>21 THE WITNESS: It seems like you are</p> <p>22 unwilling to accept what is in the report. You</p> <p>23 are asking me for an alternative, which is not</p> <p>24 necessary when the data here is very strong.</p> <p>25 BY MR. PADGETT:</p>	<p style="text-align: right;">Page 65</p> <p>1 MR. ADAMS: Object to form.</p> <p>2 THE WITNESS: So you understand I wrote</p> <p>3 this, it was sent in, and then the reports were</p> <p>4 sent to me, so therefore I had no opportunity to</p> <p>5 change it.</p> <p>6 BY MR. PADGETT:</p> <p>7 Q Are you -- you note, I think it's</p> <p>8 footnote 5 on page 10 of your report, that you had</p> <p>9 reviewed Dr. Baccarelli's report, and that you</p> <p>10 relied -- quote: I relied on Dr. Baccarelli for</p> <p>11 the limited purpose of understanding what an</p> <p>12 epidemiologist has to say on the studies and data</p> <p>13 regarding prenatal acetaminophen exposure and</p> <p>14 ASD/ADHD outcomes, period, end quote.</p> <p>15 Did I read that right?</p> <p>16 A Yes. Correct.</p> <p>17 Q Have you reached the opinions set forth</p> <p>18 in your report related to epidemiology studies</p> <p>19 based on your own independent analysis and</p> <p>20 experience reviewing epidemiology studies?</p> <p>21 A So, Counsel, as I remind you, I received</p> <p>22 Dr. Baccarelli's report afterwards, and so</p> <p>23 therefore, I did not make any changes. What is</p> <p>24 stated in my report is actually what I wrote</p> <p>25 before I even reviewed it.</p>

<p style="text-align: right;">Page 66</p> <p>1 Q I'm now a little confused. You state --</p> <p>2 in footnote 5 where you state that you reviewed --</p> <p>3 is that -- was this an amended -- part of the</p> <p>4 amended report? Because it's in your report, but</p> <p>5 you say that you received his report afterwards.</p> <p>6 Do you understand my confusion?</p> <p>7 MR. ADAMS: Object to form.</p> <p>8 THE WITNESS: It was sent to me</p> <p>9 afterwards to review, but this had already been</p> <p>10 completed.</p> <p>11 BY MR. PADGETT:</p> <p>12 Q So footnote 5 was after you had</p> <p>13 completed your report but before it was signed?</p> <p>14 MR. ADAMS: Object to form.</p> <p>15 THE WITNESS: I think the footnoting was</p> <p>16 changed, but I don't recollect that this was</p> <p>17 changed.</p> <p>18 BY MR. PADGETT:</p> <p>19 Q I guess my question is, did you review</p> <p>20 Dr. Baccarelli's report before you finalized your</p> <p>21 report?</p> <p>22 A Did I -- can you repeat again?</p> <p>23 Q Did you review Dr. Baccarelli's report,</p> <p>24 as you noted here in footnote 5, before you</p> <p>25 finalized and signed your report?</p>	<p style="text-align: right;">Page 68</p> <p>1 plaintiffs' counsel, and then you conducted your</p> <p>2 own literature search and review. Right?</p> <p>3 MR. ADAMS: Object to form.</p> <p>4 MS. KAPKE: Paragraph 16.</p> <p>5 MR. PADGETT: Paragraph 16. Sorry.</p> <p>6 THE WITNESS: I did.</p> <p>7 BY MR. PADGETT:</p> <p>8 Q Okay. And then if you could look at</p> <p>9 paragraph 21 starting with "In summary."</p> <p>10 A Where are you?</p> <p>11 Q Paragraph 21, page 7.</p> <p>12 A "In summary."</p> <p>13 Q Sort of --</p> <p>14 A Oh, okay, I see.</p> <p>15 Q If you'd take a look at that, I have a</p> <p>16 couple of questions.</p> <p>17 A (Peruses document.)</p> <p>18 Q Okay. Is this paragraph, where you're</p> <p>19 describing your reviews of the literature and</p> <p>20 priority and preference, is this specific to</p> <p>21 epidemiology studies?</p> <p>22 A I think I did that for all my studies.</p> <p>23 And you could -- if you look at my report, I go</p> <p>24 through like that in that order and evaluate it in</p> <p>25 that context. It may not be for every study, but</p>
<p style="text-align: right;">Page 67</p> <p>1 A I did review it before I signed it.</p> <p>2 Q Are you relying on Dr. Baccarelli's</p> <p>3 analysis in reaching your opinions set forth in</p> <p>4 your report?</p> <p>5 A No. But they were consistent with what</p> <p>6 I wrote earlier, because we both read the paper,</p> <p>7 utilized it -- the results, and then, you know,</p> <p>8 came to our own conclusion as to the validity of</p> <p>9 the conclusions.</p> <p>10 Q If you would turn to paragraph 15 of</p> <p>11 your report where you discuss what plaintiffs'</p> <p>12 counsel asked you to do in this case, and there it</p> <p>13 says that -- paragraph 15.</p> <p>14 A Sorry, I'm looking at page 15.</p> <p>15 Q You state there that plaintiffs' counsel</p> <p>16 gave you an initial set of literature, and then</p> <p>17 following pages 6 and 7, you indicate that you</p> <p>18 conducted your own literature search and review.</p> <p>19 Did I describe that process right?</p> <p>20 MR. ADAMS: Object to form.</p> <p>21 THE WITNESS: Can you repeat that again?</p> <p>22 Sorry, I was reading.</p> <p>23 BY MR. PADGETT:</p> <p>24 Q In paragraph 15 you indicated that you</p> <p>25 were given an initial set of materials from</p>	<p style="text-align: right;">Page 69</p> <p>1 in most studies I take that form.</p> <p>2 Q And you reference -- you use the phrase,</p> <p>3 quote, highest priority here was given a</p> <p>4 correlating, quote, clinical outcome, end quote,</p> <p>5 with drug exposure.</p> <p>6 And my question is, for purposes of this</p> <p>7 case, by "clinical outcome," do you mean the</p> <p>8 clinical diagnosis of ADHD or ASD?</p> <p>9 A Can you -- Counsel, can you identify</p> <p>10 where you're reading that from?</p> <p>11 Q You list five factors --</p> <p>12 A Uh-huh.</p> <p>13 Q -- here. Do you see that?</p> <p>14 A Mm-hmm.</p> <p>15 Q They were given the highest priority to</p> <p>16 determine the potential causal relationship, and</p> <p>17 my -- and one of these is studies correlating</p> <p>18 clinical outcome with drug exposure.</p> <p>19 Do you see that?</p> <p>20 A Yes.</p> <p>21 Q And my question is by "clinical</p> <p>22 outcome," do you mean clinical diagnosis of ADHD</p> <p>23 or ASD?</p> <p>24 A I think I -- I use those with -- with</p> <p>25 diagnoses, and I also use those that actually had</p>

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1 surveys that were validated as well.

2 Q But surveys of whether there was a

3 clinical diagnosis of ASD or ADHD, correct?

4 A Surveys that had symptomatology

5 associated with it that --

6 Q Did you give higher priority to studies

7 that involved clinical diagnoses as opposed to

8 surveys about symptomatology?

9 MR. ADAMS: Object to form.

10 THE WITNESS: So those are only one

11 factors. The factors that we looked at are -- the

12 most important is probably numbers and the

13 population and how the studies were designed.

14 So when you look at that -- well, where

15 I have diagnoses as the -- as a very important

16 factor, I think when there is a survey instrument

17 that's used and it's highly validated, you can

18 almost -- that in itself will balance it,

19 especially if the number of patients or number of

20 individuals that are evaluated could probably

21 mitigate that as well.

22 BY MR. PADGETT:

23 Q So my question is, when looking at

24 all -- all cohort numbers and experimental design

25 being equal for an epidemiology study, would you

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1 give endpoints focused on clinical diagnoses of

2 ADHD or ASD higher priority, as you put it, than

3 those looking at surveys of symptoms?

4 MR. ADAMS: Object to form.

5 THE WITNESS: In general, that would be

6 the case. But if you were to look at the total in

7 terms of the surveys -- like I said, the surveys

8 are very good instruments. Obviously when a

9 physician is diagnosing it and says that this is

10 the diagnoses or they're taking medications

11 associated, that's equally, if not stronger,

12 information.

13 BY MR. PADGETT:

14 Q You also state that -- you refer to

15 drug -- right after that, quote: Drug exposure,

16 paren, e.g., intensity of dosage or duration of

17 dosage, end quote.

18 Do you see that?

19 A Yes.

20 Q By "intensity of dosage," do you mean

21 the amount of acetaminophen taken by a pregnant

22 woman with a dose of something like Tylenol?

23 A It could be the dose that you take.

24 That's one thing. But a more important parameter

25 is the concentration. So concentration is -- is

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1 a very strong relationship in terms of dosage

2 here.

3 Q So you're talking about dose and

4 concentration that results from dose within a

5 pregnant woman's body, right?

6 A Yes. And it could also be the fetus,

7 which is the cord blood or the meconium, right.

8 Q How many epidemiology studies of those

9 you relied on for your opinions in this case have

10 data or information on the strength of doses? For

11 example, one 325-milligram caplet or two caplets

12 totaling 650 milligrams, how many epi studies have

13 that information of those you rely on in your case

14 -- in this case?

15 MR. ADAMS: Object to form.

16 THE WITNESS: So in epidemiological

17 studies, you may not capture that. But I think

18 what's very important when you look at exposure is

19 look at concentration. It's even better than --

20 than if you know the dose. The reason being is

21 just because you kick the dose doesn't mean you --

22 you have an exact amount. There's patient

23 variability, so not everybody has the same

24 exposure.

25 BY MR. PADGETT:

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1 Q Dr. Louie, my question was how many of

2 the epidemiology studies that you reviewed and

3 relied upon for your opinions in this case had the

4 dosage amount information as part of the study?

5 MR. ADAMS: Object to form.

6 THE WITNESS: So I don't think the

7 studies captured that. But having said that, they

8 have surrogate markers, and that's where most

9 studies do that. So that's not differing from

10 what the standard of practice is.

11 BY MR. PADGETT:

12 Q And by "surrogate markers," what are you

13 talking about there?

14 A You ask people for their approximate

15 dose, you survey them. You could be prospective.

16 You could be retrospective. You could also draw

17 blood.

18 Even if a person tells you that they're

19 taking X amount, they may miscode it. They may

20 say, I took 325, and then they didn't realize that

21 they took 325 of the Tylenol, but they took like,

22 say, something like NyQuil for -- and NyQuil

23 includes acetaminophen, and they don't know that.

24 So most patients don't know that.

25 Q How many epidemiology studies that you

<p style="text-align: right;">Page 74</p> <p>1 relied on for your opinions in this case had</p> <p>2 information on the number of doses taken in a day</p> <p>3 by these mothers?</p> <p>4 A I would probably have to review all --</p> <p>5 all the papers, which are not that many, like</p> <p>6 seven or eight. Do you want me to go through</p> <p>7 them?</p> <p>8 Q No, you reviewed them previously. I</p> <p>9 just -- do you recall any of these epidemiology</p> <p>10 studies that had data reflecting the number of</p> <p>11 doses taken by the mothers on --</p> <p>12 A I do have some papers. So can I use</p> <p>13 them to review if you --</p> <p>14 Q We can take a break, and if you want to</p> <p>15 review for that, you can.</p> <p>16 A No, there's no need to take a break, but</p> <p>17 I'm just saying can we -- if you want me to review</p> <p>18 it.</p> <p>19 Q Well, that takes time. Why don't we</p> <p>20 take a break and you can look at these studies</p> <p>21 or --</p> <p>22 A I don't need to take a break.</p> <p>23 MR. ADAMS: Yeah, we're not going to be</p> <p>24 doing that.</p> <p>25 BY MR. PADGETT:</p>	<p style="text-align: right;">Page 76</p> <p>1 it is a -- a chronic dose, not acute, so that is</p> <p>2 causing this.</p> <p>3 MR. ADAMS: And, Counsel, this is what I</p> <p>4 think is going to be -- is fair. To the extent</p> <p>5 you're asking him questions about these studies,</p> <p>6 he has them here. He's entitled to read them.</p> <p>7 He's not going to read them off the record. He's</p> <p>8 going to read them on the record. So if you want</p> <p>9 to ask him these general questions, and you're</p> <p>10 trying to get his memory --</p> <p>11 MR. PADGETT: Well --</p> <p>12 MR. ADAMS: Just one second, Counsel. I</p> <p>13 don't think that's fair.</p> <p>14 So allow him to look at the reports or</p> <p>15 the studies so that he can answer your question,</p> <p>16 but we'll do it on the record.</p> <p>17 MR. PADGETT: We're not going to spend</p> <p>18 time burning --</p> <p>19 MR. ADAMS: Well, then --</p> <p>20 MR. PADGETT: -- things he's already</p> <p>21 read and are in his report, so --</p> <p>22 MR. ADAMS: But he's -- you're not</p> <p>23 trying to get his memory.</p> <p>24 MR. PADGETT: We're going to get to</p> <p>25 specific studies, so you can --</p>
<p style="text-align: right;">Page 75</p> <p>1 Q Okay. As you sit here today, do you</p> <p>2 recall whether any of these epidemiology studies</p> <p>3 had data reflecting beyond perhaps days of -- that</p> <p>4 acetaminophen was taken, how many doses were taken</p> <p>5 on those particular days?</p> <p>6 A Without the papers, I recollect that</p> <p>7 that wasn't take -- captured.</p> <p>8 Q Okay. How many epidemiology studies</p> <p>9 that you relied on for your opinions in this case</p> <p>10 then reflect how many total doses -- not the</p> <p>11 number of days, but how many total doses were</p> <p>12 taken over the mother's pregnancy?</p> <p>13 MR. ADAMS: Object to form.</p> <p>14 THE WITNESS: So you're restricting my</p> <p>15 answers because you're looking for flaws of the</p> <p>16 studies. The studies actually looked at how many</p> <p>17 days they took it. That was important to them,</p> <p>18 and that to me was a very important point.</p> <p>19 I don't think because you are -- I think</p> <p>20 I said earlier that the exact doses that were</p> <p>21 taken were not there, but they did talk about the</p> <p>22 number of days of exposure. So that is also</p> <p>23 fundamentally very important because a single dose</p> <p>24 may not cause the problem, but a cumulative of</p> <p>25 doses -- in fact, I maintain in this report that</p>	<p style="text-align: right;">Page 77</p> <p>1 MR. ADAMS: All right.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q By duration -- you used the term</p> <p>4 "duration," do you mean how long over the course</p> <p>5 of the pregnancy acetaminophen was taken from the</p> <p>6 first time to the last time taken? What do you</p> <p>7 mean by "duration" there?</p> <p>8 A I think it's in each of -- it's in each</p> <p>9 of those studies, they defined it. They --</p> <p>10 they -- they categorize them in different doses in</p> <p>11 terms of how many days they've taken it. And</p> <p>12 they're not all consistent, but they're pretty</p> <p>13 close. Some may be in days. Some are in weeks.</p> <p>14 Q Did any measure -- by duration, how long</p> <p>15 from the time of the first taking of the dose to</p> <p>16 the last time a dose was taken?</p> <p>17 MR. ADAMS: Object to form.</p> <p>18 THE WITNESS: I actually don't</p> <p>19 understand the question.</p> <p>20 BY MR. PADGETT:</p> <p>21 Q You -- you testified that you saw in the</p> <p>22 studies that there are a number of days taken,</p> <p>23 some deal with number of trimesters that it was</p> <p>24 taken.</p> <p>25 Do any identify the length of time from</p>

<p style="text-align: right;">Page 78</p> <p>1 the first time taken to the last time taken during</p> <p>2 a pregnancy?</p> <p>3 MR. ADAMS: Object to form.</p> <p>4 THE WITNESS: What do you mean by the</p> <p>5 first time, the last time?</p> <p>6 BY MR. PADGETT:</p> <p>7 Q A mother could have taken one pill for</p> <p>8 five straight days, right?</p> <p>9 A Potentially.</p> <p>10 Q Yeah. Or she could have taken it five</p> <p>11 times over the course of five months, right?</p> <p>12 A Yes.</p> <p>13 Q My question is, do any of these studies</p> <p>14 identify beyond number of days or which trimester</p> <p>15 the length of time that acetaminophen was taken</p> <p>16 from the first dose to the last dose taken?</p> <p>17 MR. ADAMS: Object to form.</p> <p>18 THE WITNESS: Some of these studies</p> <p>19 stratify the trimesters. So therefore if you're</p> <p>20 looking at that, yeah, it does give you a little</p> <p>21 insight as to where it is.</p> <p>22 BY MR. PADGETT:</p> <p>23 Q As far as whether it was taken in a</p> <p>24 particular trimester.</p> <p>25 A Correct.</p>	<p style="text-align: right;">Page 80</p> <p>1 Q And for mice, you used -- you gave more</p> <p>2 weight to studies that involved doses below 150</p> <p>3 milligrams per kilogram, correct?</p> <p>4 A In general, yes.</p> <p>5 Q Did you exclude any articles relating to</p> <p>6 humans that involved a dose above the therapeutic</p> <p>7 range?</p> <p>8 A I think I considered acute doses, but I</p> <p>9 weighed them very lowly because I know that</p> <p>10 there -- there may be confounding issues.</p> <p>11 Q What do you mean by "confounding</p> <p>12 issues"?</p> <p>13 A If you use -- let's say you try to</p> <p>14 commit suicide. I may have looked at the paper; I</p> <p>15 may have reviewed it. I probably did not include</p> <p>16 it into this report. In fact, I'm not sure -- but</p> <p>17 I'm pretty sure I didn't include it because I see</p> <p>18 the -- that there is probably other confounding</p> <p>19 factors that may -- may confuse me.</p> <p>20 Q Do you recall the Leung, L-E-U-N-G, 2012</p> <p>21 study?</p> <p>22 A There's -- there's several Leungs, so</p> <p>23 therefore I'm a little bit...</p> <p>24 Q Do you -- do you recall a study that</p> <p>25 involved middle age onset cirrhosis that you</p>
<p style="text-align: right;">Page 79</p> <p>1 Q Okay. In your literature search, did --</p> <p>2 and your analysis, did you exclude any animal</p> <p>3 studies assessing a dose above the equivalent of</p> <p>4 the human therapeutic range in rodents?</p> <p>5 A Did I ex- -- can you say that again?</p> <p>6 Q Did you exclude any animal studies</p> <p>7 assessing a dose that is above the equivalent of a</p> <p>8 human therapeutic range in rodents?</p> <p>9 MR. ADAMS: Object to form.</p> <p>10 THE WITNESS: So the question is -- is</p> <p>11 very different because rats are more resistant</p> <p>12 than mice, so therefore, you need to be --</p> <p>13 probably because the translation between a rat and</p> <p>14 a human may be different from that of a mice and a</p> <p>15 human.</p> <p>16 BY MR. PADGETT:</p> <p>17 Q Did you exclude any studies based on the</p> <p>18 level of dosing used in an animal study?</p> <p>19 A I probably considered it, but I gave it</p> <p>20 heavier weight on those that were -- for that</p> <p>21 animal species that were subhepatic toxic.</p> <p>22 Q So for rats, you gave greater weight to</p> <p>23 those involving doses below 500 milligrams per</p> <p>24 kilogram, correct?</p> <p>25 A It was more translatable for me.</p>	<p style="text-align: right;">Page 81</p> <p>1 relied on, the Leung 2012?</p> <p>2 MR. ADAMS: Object to form.</p> <p>3 THE WITNESS: I see that you have the</p> <p>4 paper. Can I see it?</p> <p>5 MS. KAPKE: This will be Exhibit 22.</p> <p>6 MR. ADAMS: Oh, it should be actually</p> <p>7 23. You marked the rebuttal as 22.</p> <p>8 MS. KAPKE: Oh, yeah.</p> <p>9 (Exhibit No. 23 was marked for</p> <p>10 identification.)</p> <p>11 BY MR. PADGETT:</p> <p>12 Q Dr. Louie, I hand you what's been marked</p> <p>13 as Exhibit 23, which is the Leung study we were</p> <p>14 discussing.</p> <p>15 As mentioned, this study involved</p> <p>16 acetaminophen and middle age onset biliary</p> <p>17 cirrhosis. Right?</p> <p>18 A Let me read it -- oh, what the</p> <p>19 title says -- that's what the title say.</p> <p>20 Q And if you turn to 579, the third page</p> <p>21 of this, it talks about an effect seen in patients</p> <p>22 with primary biliary cirrhosis poisoned by</p> <p>23 ingesting excessive amounts of acetaminophen. Is</p> <p>24 that right?</p> <p>25 A Where are you reading this?</p>

<p style="text-align: right;">Page 82</p> <p>1 Q On the right-hand column, and it says</p> <p>2 about halfway down, "In particular."</p> <p>3 A I do.</p> <p>4 Q Okay. This study involved looking at</p> <p>5 toxic overdoses of acetaminophen, right?</p> <p>6 MR. ADAMS: Object to form.</p> <p>7 THE WITNESS: It did not say that. I</p> <p>8 will read it for you. It says --</p> <p>9 MR. ADAMS: Wait just one second.</p> <p>10 There's a question -- he asks questions, you</p> <p>11 answer questions. Just let him ask another</p> <p>12 question.</p> <p>13 BY MR. PADGETT:</p> <p>14 Q Poisoned, I guess. Toxic poisoning. I</p> <p>15 guess -- and if you look at the abstract, it says</p> <p>16 "excessive amounts of acetaminophen."</p> <p>17 A The paper says "ingesting excessive</p> <p>18 amounts." There was no poison in it.</p> <p>19 Q Well, if you look at -- there at</p> <p>20 page 579, it says that it found in almost 35</p> <p>21 percent of individuals poisoned by ingesting</p> <p>22 excessive amounts of acetaminophen. Right?</p> <p>23 A It did not give a dose, so I don't know</p> <p>24 if I know that.</p> <p>25 Q Okay. But you included this, though, in</p>	<p style="text-align: right;">Page 84</p> <p>1 A Yes.</p> <p>2 Q Okay. Is it your opinion that relevant</p> <p>3 regulatory guidelines do not establish a</p> <p>4 sufficient standard of scientific reliability?</p> <p>5 MR. ADAMS: Object to form.</p> <p>6 THE WITNESS: I'm sorry, I don't</p> <p>7 understand that question at all.</p> <p>8 BY MR. PADGETT:</p> <p>9 Q You said that there have been calls for</p> <p>10 the FDA and other regulatory agencies to provide</p> <p>11 updated recommendations.</p> <p>12 And my question is, is it your opinion</p> <p>13 that relevant FDA regulatory guidelines do not</p> <p>14 establish a sufficient standard of scientific</p> <p>15 reliability?</p> <p>16 MR. ADAMS: Object to form.</p> <p>17 THE WITNESS: Can you rephrase that?</p> <p>18 MR. PADGETT: Can you read it back?</p> <p>19 THE REPORTER: "You said that there have</p> <p>20 been calls for the FDA and other regulatory</p> <p>21 agencies to provide updated recommendations.</p> <p>22 "And my question is, is it your opinion</p> <p>23 that relevant FDA regulatory guidelines do not</p> <p>24 establish a sufficient standard of scientific</p> <p>25 reliability?"</p>
<p style="text-align: right;">Page 83</p> <p>1 your analysis for purposes of your report, right?</p> <p>2 A I did.</p> <p>3 Q Okay. And on page 18 of your report,</p> <p>4 you describe a number of studies on association</p> <p>5 between ASD and ADHD, and you -- you want to go to</p> <p>6 page 18 of your report?</p> <p>7 MR. ADAMS: He's on the report now.</p> <p>8 THE WITNESS: Oh, I'm sorry. I just --</p> <p>9 MR. ADAMS: No, no, no. He's on your</p> <p>10 report.</p> <p>11 THE WITNESS: Okay. 18.</p> <p>12 BY MR. PADGETT:</p> <p>13 Q Okay. You note -- there's a reference</p> <p>14 there on page 18, it's the last line, and you</p> <p>15 reference that studies relating to acetaminophen</p> <p>16 and ASD have led to calls for the FDA and other</p> <p>17 regulatory agencies to provide updated</p> <p>18 recommendations."</p> <p>19 Do you see that?</p> <p>20 A Are you talking about third from the</p> <p>21 bottom?</p> <p>22 Q The last sentence on page -- on page 18.</p> <p>23 A Yes.</p> <p>24 Q Okay. Is it -- and you've done work</p> <p>25 with the FDA, right? For the FDA.</p>	<p style="text-align: right;">Page 85</p> <p>1 MR. ADAMS: Object to form.</p> <p>2 THE WITNESS: You -- you're asking me to</p> <p>3 conclude something that you said. Right?</p> <p>4 You're --</p> <p>5 BY MR. PADGETT:</p> <p>6 Q Let me ask you this: Do you believe</p> <p>7 that FDA regulatory guidelines provide a</p> <p>8 sufficient standard of scientific reliability?</p> <p>9 A They -- they would try to use the data</p> <p>10 that is available to come to a recommendation.</p> <p>11 Q You discuss some prevalence and</p> <p>12 incidence issues in your report at pages 19</p> <p>13 through 21. Do you recall that? If you could</p> <p>14 turn there.</p> <p>15 A I give a highlight of what is in the</p> <p>16 literature.</p> <p>17 Q Okay. As a pharmacologist, how often</p> <p>18 have you analyzed the comparative prevalence of</p> <p>19 diagnoses of conditions between countries?</p> <p>20 A I do it when I was advisor to the NIH,</p> <p>21 probably about four years.</p> <p>22 Q And what conditions were at issue there?</p> <p>23 A TB, HIV prevalence, toxic effects of</p> <p>24 treatment in Thais versus Americans, very</p> <p>25 different.</p>

<p style="text-align: right;">Page 86</p> <p>1 Q And then there's -- I noticed in your</p> <p>2 list of materials reviewed, you -- there are</p> <p>3 various deposition transcripts of Johnson &</p> <p>4 Johnson Consumer, Inc., witnesses in your list of</p> <p>5 materials.</p> <p>6 Are you relying on any way on those</p> <p>7 depositions for your opinions in this case?</p> <p>8 A Not at all. I think I got copies of</p> <p>9 them, and to be -- so therefore I added them.</p> <p>10 Q But you're not relying on them?</p> <p>11 A No.</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 BY MR. PADGETT:</p> <p>14 Q Is that a "no"?</p> <p>15 A No, I did not rely on them.</p> <p>16 Q Okay. Turn to page 9 of your report,</p> <p>17 your summary of opinions.</p> <p>18 If you could look at paragraph 27 and</p> <p>19 review that. I've got a couple of questions.</p> <p>20 A (Peruses document.)</p> <p>21 Q There you state the opinion that:</p> <p>22 "Prenatal exposure to acetaminophen increases the</p> <p>23 risk of developing ASD and ADHD in offspring when</p> <p>24 acetaminophen is taken by the pregnant mother in</p> <p>25 the therapeutic dose range, which per Tylenol</p>	<p style="text-align: right;">Page 88</p> <p>1 MR. ADAMS: Object to form.</p> <p>2 THE WITNESS: I don't think I actually</p> <p>3 stated that. It just talks about the 28 days</p> <p>4 throughout the pregnancy.</p> <p>5 BY MR. PADGETT:</p> <p>6 Q Right. But my question is, does it</p> <p>7 matter to you whether it's 28 consecutive days or</p> <p>8 whether it -- the 28 days are spaced out evenly</p> <p>9 over the entire pregnancy?</p> <p>10 MR. ADAMS: Object to form.</p> <p>11 THE WITNESS: I don't think I made that</p> <p>12 as a consideration.</p> <p>13 BY MR. PADGETT:</p> <p>14 Q Okay. So it's just -- your opinion is</p> <p>15 the increased risk is 28 days, period, regardless</p> <p>16 of whether it's 28 straight days or 28 days spread</p> <p>17 out evenly over the pregnancy.</p> <p>18 MR. ADAMS: Object to form.</p> <p>19 THE WITNESS: To be specific, it says</p> <p>20 for at least for 28 days. So I'm not restricting</p> <p>21 it to just 28 days.</p> <p>22 BY MR. PADGETT:</p> <p>23 Q It could be more, right?</p> <p>24 A Okay. Yeah.</p> <p>25 Q Whether it's 28 days or 50 days, did you</p>
<p style="text-align: right;">Page 87</p> <p>1 label is 0.65 grams or 650 milligrams and 4 grams,</p> <p>2 4,000 milligrams per day, for at least 28</p> <p>3 cumulative days during pregnancy for a total of</p> <p>4 between 18.2 grams or 18,200 milligrams to 112</p> <p>5 grams or 112,000 milligrams."</p> <p>6 Did I read that correctly?</p> <p>7 A It appears so.</p> <p>8 Q So does that 650-milligram number assume</p> <p>9 two 325-milligram caplets?</p> <p>10 A Or tablets or liquid.</p> <p>11 Q Okay. And the 4,000 milligrams assumes</p> <p>12 daily maximum doses of 1,000 milligrams, taking</p> <p>13 500 milligram max tablets or caplets; is that</p> <p>14 right?</p> <p>15 A Or you could take it -- liquid capsules,</p> <p>16 two six times a day.</p> <p>17 Q So there's a number of different ways --</p> <p>18 A Yeah.</p> <p>19 Q -- that they could be taken on</p> <p>20 various -- at various times, right?</p> <p>21 A Yeah. It depends on the dosage form and</p> <p>22 how you take it.</p> <p>23 Q Okay. With your opinion that says 28</p> <p>24 cumulative days during pregnancy, does it matter</p> <p>25 if the 28 days are 28 consecutive days?</p>	<p style="text-align: right;">Page 89</p> <p>1 consider whether, in reaching your opinion, it was</p> <p>2 consecutive days or days spread out evenly over</p> <p>3 the course of the pregnancy?</p> <p>4 MR. ADAMS: Object to form.</p> <p>5 THE WITNESS: I think the data -- I used</p> <p>6 the data to back this up, and so it didn't matter.</p> <p>7 BY MR. PADGETT:</p> <p>8 Q It didn't matter. Okay.</p> <p>9 What about does it matter when the doses</p> <p>10 were taken during the pregnancy with regard to</p> <p>11 your 28 days opinion?</p> <p>12 A In the studies, the data was captured</p> <p>13 relatively poorly, but it's -- it stated that you</p> <p>14 have increased risks if you have two trimesters,</p> <p>15 and -- but you still have one trimester that's --</p> <p>16 that had those effects as well.</p> <p>17 Q What do you mean by you still have one</p> <p>18 trimester that still --</p> <p>19 A So if you took it in one trimester, you</p> <p>20 still saw a signal.</p> <p>21 Q What do you mean by "signal"?</p> <p>22 A Increased risk of ADSD -- ASD-ADHD.</p> <p>23 Q Okay. What if all 28 days that you're</p> <p>24 talking about here are during the first month</p> <p>25 after conception, is it still an increased risk in</p>

<p style="text-align: right;">Page 90</p> <p>1 your opinion?</p> <p>2 MR. ADAMS: Object to form.</p> <p>3 THE WITNESS: I don't think that's in my</p> <p>4 opinion here. My opinion -- my opinion was just a</p> <p>5 broad 28 days.</p> <p>6 BY MR. PADGETT:</p> <p>7 Q And that's my question. Does it matter</p> <p>8 if those 28 days all occur in the first month</p> <p>9 after conception? Is it still your opinion that</p> <p>10 there's an increased risk?</p> <p>11 MR. ADAMS: Object to form.</p> <p>12 THE WITNESS: In my summary opinion, I</p> <p>13 did not -- I did not speculate, nor did I add</p> <p>14 that. So it's at least for 28 days. It didn't</p> <p>15 talk about how you spread it out.</p> <p>16 BY MR. PADGETT:</p> <p>17 Q Okay. Would you agree that much of the</p> <p>18 human fetal brain, including the cerebellum and</p> <p>19 hippocampus, has not even formed in the first 28</p> <p>20 days of gestation?</p> <p>21 A I don't know if I would agree. That's</p> <p>22 why you -- I don't know if I agree with that.</p> <p>23 Q Okay. Has the cerebellum and the</p> <p>24 hippocampus been formed within the first 28 days</p> <p>25 of gestation?</p>	<p style="text-align: right;">Page 92</p> <p>1 MR. PADGETT: Okay. Just object to</p> <p>2 form.</p> <p>3 MR. ADAMS: I will. I will.</p> <p>4 Wait, I'm agreeing with you that I will</p> <p>5 object to form. One lawyer.</p> <p>6 MR. PADGETT: Sure.</p> <p>7 MR. ADAMS: Thank you.</p> <p>8 THE REPORTER: "Has the cerebellum and</p> <p>9 the hippocampus been formed within the first --</p> <p>10 first 28 days of gestation?"</p> <p>11 MR. ADAMS: Object to form.</p> <p>12 THE WITNESS: It is not, but that</p> <p>13 doesn't mean that the drug can't affect stem cells</p> <p>14 that will eventually form the brain. So you have</p> <p>15 to remember stem cells eventually become</p> <p>16 developed.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q Does your report say anything about the</p> <p>19 impact of acetaminophen on stem cells?</p> <p>20 A You asked me a question if -- if the</p> <p>21 cerebellum is formed, but the cells before it</p> <p>22 forms are the stem cells that form it. So...</p> <p>23 Q My question is, does your report say</p> <p>24 anything about the impact of acetaminophen on stem</p> <p>25 cells?</p>
<p style="text-align: right;">Page 91</p> <p>1 MR. ADAMS: Object to form.</p> <p>2 THE WITNESS: Just because it's not</p> <p>3 formed doesn't mean --</p> <p>4 MR. ADAMS: No, no, no. He asked a</p> <p>5 question, and you're answering a different</p> <p>6 question now. Answer his question.</p> <p>7 MS. RICHER: Counsel, you don't need to</p> <p>8 make speaking objections.</p> <p>9 MR. PADGETT: Yes, it's -- it's getting</p> <p>10 old.</p> <p>11 MR. ADAMS: It's not old; it's anew.</p> <p>12 I'm trying to make the record fair, and I'm trying</p> <p>13 to do that so we can move forward --</p> <p>14 MR. PADGETT: Can you read my question</p> <p>15 back, please.</p> <p>16 MR. ADAMS: And by the way, we've got,</p> <p>17 you know, one lawyer.</p> <p>18 MS. RICHER: Well, pick which part of</p> <p>19 the deposition protocol you're going to follow.</p> <p>20 MR. ADAMS: One more time, we've got one</p> <p>21 lawyer.</p> <p>22 MS. RICHER: Pick which parts of the</p> <p>23 deposition protocol you're going to follow, and --</p> <p>24 MR. ADAMS: One more time, we've got one</p> <p>25 lawyer. Yes.</p>	<p style="text-align: right;">Page 93</p> <p>1 A It does not, but it -- I'm addressing</p> <p>2 your question.</p> <p>3 Q If a mother in one of these epi studies</p> <p>4 you reviewed reported she took acetaminophen on 28</p> <p>5 days, but on each of those days she only took one</p> <p>6 325-milligram caplet or tablet for a slight</p> <p>7 headache, would that still meet your 28 days'</p> <p>8 threshold for your opinion?</p> <p>9 MR. ADAMS: Object to form.</p> <p>10 THE WITNESS: Counsel, you're asking me</p> <p>11 to speculate.</p> <p>12 BY MR. PADGETT:</p> <p>13 Q I'm not -- you have 650 -- you have a</p> <p>14 total of 18.2 grams to 112 grams based on at least</p> <p>15 cumulative -- 28 cumulative days or a total of</p> <p>16 18.2 grams to 112 grams for increased risk.</p> <p>17 Right?</p> <p>18 A Yes, I wrote that because the labeling</p> <p>19 has changed. When I was -- let's say ten years</p> <p>20 ago, it was 325. So I'm complying with the</p> <p>21 labeling, so therefore, patients can take 325.</p> <p>22 Q Okay. My question is, if a woman took</p> <p>23 one 325-milligram caplet on each of those 28 days,</p> <p>24 would that still meet your threshold for an</p> <p>25 increased risk?</p>

<p>Page 94</p> <p>1 MR. ADAMS: Object to form.</p> <p>2 THE WITNESS: The data was captured, did</p> <p>3 she take it or not regardless of dosage.</p> <p>4 BY MR. PADGETT:</p> <p>5 Q Okay. So --</p> <p>6 MR. ADAMS: Before you ask your next</p> <p>7 question, and I'm not going to stop you from</p> <p>8 asking it, but in order for us to get lunch in on</p> <p>9 time, we've got to get it in before --</p> <p>10 MS. KAPKE: Let's go off the record.</p> <p>11 MR. ADAMS: Oh, I'm sorry.</p> <p>12 MR. PADGETT: Yes, let's go off the</p> <p>13 record.</p> <p>14 THE VIDEOGRAPHER: We're going off the</p> <p>15 video record at 11:05 a.m.</p> <p>16 (Recess.)</p> <p>17 THE VIDEOGRAPHER: We are going back on</p> <p>18 the video record at 11:19 a.m.</p> <p>19 MR. PADGETT: Just briefly, I would kind</p> <p>20 of like to comment on I've been very, very</p> <p>21 patient, Julien, but 90 percent of the questions</p> <p>22 I've asked, and we're almost two hours in now,</p> <p>23 he's basically avoiding, refusing to answer, but</p> <p>24 then in turn, you -- instead of pursuant to the</p> <p>25 deposition protocol, you're not objecting to form</p>	<p>Page 96</p> <p>1 detail, but --</p> <p>2 MR. ADAMS: Counsel, why did you waste</p> <p>3 the time on the record about studies.</p> <p>4 MR. PADGETT: Go ahead. I'm curious.</p> <p>5 MR. ADAMS: I just want to know why did</p> <p>6 you waste time on the record for this?</p> <p>7 MR. PADGETT: Okay. Do you -- is it --</p> <p>8 is the protocol object to form only?</p> <p>9 MR. ADAMS: All right. No, so let me</p> <p>10 respond to you. When you suggest that it's</p> <p>11 90 percent of the time he's not answering, that's</p> <p>12 not accurate.</p> <p>13 To the extent that I've not objected to</p> <p>14 form and said other things, it's because I'm</p> <p>15 trying to get an answer to the question, not</p> <p>16 something other than that. All right.</p> <p>17 And I'm certain that none of this is</p> <p>18 going to see the light of day because I will</p> <p>19 continue to just object to form from now on.</p> <p>20 MR. PADGETT: Great.</p> <p>21 MR. ADAMS: But what -- what I don't</p> <p>22 appreciate is you putting something on this record</p> <p>23 that is not accurate. All right?</p> <p>24 So let's move on.</p> <p>25 MR. PADGETT: Great.</p>
<p>Page 95</p> <p>1 only, and you're coaching, speaking objections.</p> <p>2 That -- that needs to stop, and we need to follow</p> <p>3 the protocol.</p> <p>4 And if he -- he can answer my question,</p> <p>5 he can answer my question. If he can't answer it,</p> <p>6 then he says he can -- he can say, "I don't know"</p> <p>7 or "I can't answer that question."</p> <p>8 But we're willing to go to the Court,</p> <p>9 suspend if we keep getting kind of the</p> <p>10 obstructionist approach that we're seeing today</p> <p>11 with these questions. So I just wanted to make</p> <p>12 that clear.</p> <p>13 The other thing is that if he needs to</p> <p>14 see a study, he can tell us which study. If he</p> <p>15 wants to review it, we can go off the record, but</p> <p>16 we're not going to spend all day taking record</p> <p>17 time for him to review studies. That was how it</p> <p>18 was handled in Cabrera. When he needed some time,</p> <p>19 Dr. Cabrera went off the record and reviewed</p> <p>20 studies, and that's what we're going to do.</p> <p>21 So I just want to kind of make that</p> <p>22 clear. Let's stay with the deposition protocol,</p> <p>23 number one. And number two, we don't need to go</p> <p>24 on -- stay on the record if he wants to look at a</p> <p>25 study. We're going to get into the studies in</p>	<p>Page 97</p> <p>1 BY MR. PADGETT:</p> <p>2 Q Dr. Louie, from these epi studies you</p> <p>3 reviewed, you can't tell whether a mother</p> <p>4 sporadically took a 325 single -- a 325-milligram</p> <p>5 single caplet or tablet one day for a slight</p> <p>6 headache or a couple of doses of two caplets for</p> <p>7 650 milligrams for fever on another day, right?</p> <p>8 A I think the -- since you -- it's a</p> <p>9 pretty large -- well, seven studies. Some did</p> <p>10 capture it. Some did -- some of the studies</p> <p>11 captured it.</p> <p>12 Q Captured what?</p> <p>13 A That they used it for fever. They used</p> <p>14 it for headaches and things like that. So that</p> <p>15 was captured.</p> <p>16 Q But they didn't capture the dosage</p> <p>17 amounts, right?</p> <p>18 A I don't believe that they were in the --</p> <p>19 described.</p> <p>20 Q And if the full maximum dose of four</p> <p>21 times 1000 milligrams was taken for five days over</p> <p>22 the pregnancy, that would be 20 grams total,</p> <p>23 right?</p> <p>24 A Four grams times five, yes.</p> <p>25 Q Okay. And even though that's more than</p>

<p style="text-align: right;">Page 98</p> <p>1 18.2 grams, generally, which you refer to your</p> <p>2 opinion, it's your opinion that 18.2 grams taken</p> <p>3 over 28 days results in a twofold risk, while 20</p> <p>4 grams over five days does not?</p> <p>5 Is that -- am I understanding your</p> <p>6 opinion right?</p> <p>7 MR. ADAMS: Object to form.</p> <p>8 THE WITNESS: Can -- can you restate</p> <p>9 that?</p> <p>10 BY MR. PADGETT:</p> <p>11 Q Is your opinion that it has to be 28</p> <p>12 day -- days -- cumulative days at any dose or</p> <p>13 these 18.2 to 112 grams that you have here?</p> <p>14 MR. ADAMS: Object to form.</p> <p>15 THE WITNESS: Well, I gave you a range</p> <p>16 here, so that's sort of self-explanatory.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q Would 14,000 milligrams taken for five</p> <p>19 days not qualify for the increased risk that you</p> <p>20 set forth in your report?</p> <p>21 MR. ADAMS: Object to form.</p> <p>22 THE WITNESS: I don't think that's how</p> <p>23 it was phrased.</p> <p>24 BY MR. PADGETT:</p> <p>25 Q You say at least 28 days -- cumulative</p>	<p style="text-align: right;">Page 100</p> <p>1 MR. ADAMS: Object to form.</p> <p>2 THE WITNESS: I don't think that's what</p> <p>3 I said.</p> <p>4 BY MR. PADGETT:</p> <p>5 Q I'm asking you if that would meet -- the</p> <p>6 five days at 4,000 milligrams would meet your</p> <p>7 opinion on increased risk that you set forth here</p> <p>8 in paragraph 27 of your report.</p> <p>9 MR. ADAMS: Object to form.</p> <p>10 THE WITNESS: I -- I think what I'm</p> <p>11 stating here is 28 days of the pregnancy. The</p> <p>12 dosage -- so you're saying if -- I'm trying to</p> <p>13 understand the math. That's what I'm trying to --</p> <p>14 you're giving me a mathematical question, right?</p> <p>15 BY MR. PADGETT:</p> <p>16 Q It's not a math -- you've already</p> <p>17 calculated the math, Dr. Louie. Five grams --</p> <p>18 five days, 4,000 milligrams is 20 grams. We've</p> <p>19 established that.</p> <p>20 My question is, does five days of taking</p> <p>21 acetaminophen at the maximum dose of 4,000</p> <p>22 milligrams, is -- does that meet your opinion of</p> <p>23 28 days cumulative doses results in an increased</p> <p>24 risk of ASD or ADHD?</p> <p>25 MR. ADAMS: Object to form.</p>
<p style="text-align: right;">Page 99</p> <p>1 days during pregnancy or a total of between 18.2</p> <p>2 grams to 112 grams, right?</p> <p>3 A I'm sorry. I'm still one -- one</p> <p>4 question back. Can you repeat your question</p> <p>5 again?</p> <p>6 BY MR. PADGETT:</p> <p>7 Q Does 4,000 milligrams taken on just five</p> <p>8 days, and that would be 20 grams, fall within your</p> <p>9 opinion of an increased risk of 28 cumulative days</p> <p>10 during pregnancy or a total of 18.2 grams to 112</p> <p>11 grams?</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 THE WITNESS: I think what I'm saying is</p> <p>14 you have 28 days of self-exposure. The dose can</p> <p>15 range from this. I don't think I can limit it.</p> <p>16 BY MR. PADGETT:</p> <p>17 Q But you need 28 cumulative days of</p> <p>18 exposure. Agreed?</p> <p>19 MR. ADAMS: Object to form.</p> <p>20 BY MR. PADGETT:</p> <p>21 Q That's your opinion.</p> <p>22 A At least 28 days of exposure.</p> <p>23 Q Okay. So if a woman takes five days at</p> <p>24 4,000 milligrams, that would not meet your opinion</p> <p>25 with regard to an increased risk; is that correct?</p>	<p style="text-align: right;">Page 101</p> <p>1 THE WITNESS: So what you're trying to</p> <p>2 say here is instead of making it "or," you're</p> <p>3 making it "and" to my opinion.</p> <p>4 BY MR. PADGETT:</p> <p>5 Q That's what I'm trying to get at,</p> <p>6 Dr. Louie.</p> <p>7 A Oh, you could tell me that so I would be</p> <p>8 clear to understand your question because I was</p> <p>9 trying to figure out what you were trying to tell</p> <p>10 me.</p> <p>11 Q I -- I gave you a hypothetical, and you</p> <p>12 need to answer a hypothetical question.</p> <p>13 Would five days, 4,000 milligrams, which</p> <p>14 would total 20 grams of acetaminophen, meet your</p> <p>15 definition of an increased risk in paragraph 27?</p> <p>16 A So I --</p> <p>17 MR. ADAMS: One second. Object to form.</p> <p>18 THE WITNESS: I think I've already</p> <p>19 answered you that this is an "or," not an "and."</p> <p>20 BY MR. PADGETT:</p> <p>21 Q Dr. Louie, does that scenario meet your</p> <p>22 definition of the increased risk set forth in</p> <p>23 paragraph 27 of 28 days or 18.2 grams to 112</p> <p>24 grams?</p> <p>25 A Can I review one of the papers? Sorry.</p>

<p style="text-align: right;">Page 102</p> <p>1 MR. ADAMS: I'm going to object to form.</p> <p>2 THE WITNESS: Can I review my -- the</p> <p>3 papers?</p> <p>4 MR. PADGETT: Let's go off the record.</p> <p>5 Go ahead.</p> <p>6 THE VIDEOGRAPHER: We're going off the</p> <p>7 video record at 11:28 a.m.</p> <p>8 (Pause in the proceedings.)</p> <p>9 THE VIDEOGRAPHER: We are going back on</p> <p>10 the video record at 11:31 a.m.</p> <p>11 BY MR. PADGETT:</p> <p>12 Q Dr. Louie, my question was, if a</p> <p>13 woman -- if a pregnant woman takes acetaminophen</p> <p>14 on five days during the course of her pregnancy at</p> <p>15 the max dose of 4,000 milligrams per day totaling</p> <p>16 20 grams, as we discussed, does that meet the</p> <p>17 definition that you put forth in paragraph 27 of</p> <p>18 an increased risk of at least 28 cumulative days</p> <p>19 during the pregnancy or a total between 18.2 or</p> <p>20 112 grams?</p> <p>21 MR. ADAMS: Object to form.</p> <p>22 THE WITNESS: So in the studies exposure</p> <p>23 of up to, let's say, one week show the signal of</p> <p>24 hyperkinetic significance. So when you limit it</p> <p>25 to five, that may be one issue, but if you</p>	<p style="text-align: right;">Page 104</p> <p>1 A Now you have a compound question. Can</p> <p>2 you break it down?</p> <p>3 Q Do any of the studies you reviewed</p> <p>4 support an association with five days of</p> <p>5 therapeutic dose and a twofold increased risk for</p> <p>6 being diagnosed with ASD?</p> <p>7 A So I'll answer in two parts because you</p> <p>8 asked two questions.</p> <p>9 First, you asked five days. There was</p> <p>10 no bucket of five days. The bucket was one week</p> <p>11 and weeks. So therefore, to answer -- if your</p> <p>12 five days fit that, yes.</p> <p>13 2X, you're talking about twofold. So</p> <p>14 you don't need a twofold to be statistically</p> <p>15 significant.</p> <p>16 Q Your opinion, though, is a twofold</p> <p>17 increased risk, right?</p> <p>18 MR. ADAMS: Object to form.</p> <p>19 BY MR. PADGETT:</p> <p>20 Q Paragraph 28 of your report.</p> <p>21 A It says specifically "at least 28 days."</p> <p>22 Right?</p> <p>23 So in the therapeutic range set forth</p> <p>24 above for at least 28 days during the pregnancy.</p> <p>25 So therefore, if you expand it to 28 days, yeah,</p>
<p style="text-align: right;">Page 103</p> <p>1 limit -- if you go to one week, we saw a signal.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q When you say "a signal," what do you</p> <p>4 mean?</p> <p>5 A Increase in the hazard ratio or the</p> <p>6 relative risk or, you know, odds ratios.</p> <p>7 Q And by -- are you referring to one of</p> <p>8 the Liew studies when you're talking about the</p> <p>9 hyperkinetic relationship for -- for one week?</p> <p>10 A Yes.</p> <p>11 Q And we'll get to that.</p> <p>12 Which -- which studies did you just</p> <p>13 review?</p> <p>14 A The Liew 2014, Liew 2016, and Istrom</p> <p>15 (phonetic).</p> <p>16 Q Oh, Ystrom.</p> <p>17 A Oh, I thought you put an "I" --</p> <p>18 Q And which one showed an association,</p> <p>19 according to your review, for one week?</p> <p>20 A Because you even said it, so it came</p> <p>21 from Liew.</p> <p>22 Q Okay. Do any studies support that five</p> <p>23 days of therapeutic dose levels during a pregnancy</p> <p>24 have found a twofold increased risk for being</p> <p>25 diagnosed with ASD or ADHD?</p>	<p style="text-align: right;">Page 105</p> <p>1 that is -- there is signals for 2.0.</p> <p>2 Q But five days -- you set the threshold</p> <p>3 at 28 days. Does five days of 4,000 milligrams</p> <p>4 meet your definition of an increased risk for ASD?</p> <p>5 MR. ADAMS: Object to form.</p> <p>6 THE WITNESS: So -- so I set the -- a</p> <p>7 very conservative exposure. However, there are</p> <p>8 studies from the epidemiology studies that shows</p> <p>9 that lower levels of exposure could give you a</p> <p>10 statistical risk -- an increased risk.</p> <p>11 BY MR. PADGETT:</p> <p>12 Q "May" was your -- lower than 28 days was</p> <p>13 the language you used, right?</p> <p>14 A I used "may," but the paper says -- the</p> <p>15 scientific data says "is" because they show the</p> <p>16 data.</p> <p>17 Q Is it your opinion that if the lowest</p> <p>18 dose -- full dose of 650 milligrams is taken on</p> <p>19 every one of the 28 days by a mother, and those</p> <p>20 doses are evenly spaced over the entire pregnancy,</p> <p>21 that is still an increased risk in your opinion?</p> <p>22 MR. ADAMS: Object to form.</p> <p>23 THE WITNESS: So when you -- would it be</p> <p>24 fair for you to read that question?</p> <p>25 MR. PADGETT: Go ahead and read it,</p>

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1 please.

2 THE REPORTER: "Is it your opinion that

3 if the lowest dose -- full dose of 650 milligrams

4 is taken on every one of the 28 days by a mother,

5 and those doses are evenly spaced over the entire

6 pregnancy, that is still an increased risk in your

7 opinion?"

8 THE WITNESS: I believe that's what my

9 opinion is.

10 BY MR. PADGETT:

11 Q Okay. If a woman takes -- we still

12 haven't answered this.

13 If a woman takes a 4,000-milligram dose

14 for only five days over the course of her

15 pregnancy, is that a twofold increased risk as set

16 forth in paragraph 27 of your report?

17 MR. ADAMS: Object to form.

18 BY MR. PADGETT:

19 Q Or 27, 28.

20 MR. ADAMS: Same objection.

21 THE WITNESS: No, you rephrased it as

22 five days, four grams a day, 20 grams, and so

23 therefore it's in the bucket.

24 But then what you didn't do is that I

25 didn't say five days. But in one week -- if I

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1 remember correctly, if I may go back -- that there

2 was a statistical significance, and it's not

3 twofold but it's the statistical significance

4 hazard ratio.

5 BY MR. PADGETT:

6 Q Of one week. And we'll get to that.

7 A Yeah, one week.

8 Q In paragraph 29 of your report, you

9 state: "The reason for this increased risk is

10 that acetaminophen and its metabolites can deplete

11 glutathione" --

12 Can we agree to GSH --

13 A Sure.

14 Q -- for glutathione?

15 -- "thereby causing oxidative stress

16 systematically and in the brain." And number (ii)

17 "NAPQI and its adducts can induce oxidative

18 stress, immune reactivity and inflammation."

19 Did I read that right?

20 A You did.

21 Q And your opinion is that both -- that

22 these molecular mechanisms of action increase the

23 risk of -- of -- both of these molecular

24 mechanisms of action increase the risk of ASD/ADHD

25 development, end quote; is that right?

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1 A That's what I stated there, yeah.

2 Q And is it your opinion that even if 18.2

3 grams of acetaminophen are taken over the duration

4 of the entire pregnancy and evenly spaced out

5 equal doses of 650 milligrams, that leads to a

6 twofold increased risk for ASD and -- or ADHD?

7 MR. ADAMS: Object to form.

8 THE WITNESS: For 28 days?

9 BY MR. PADGETT:

10 Q Yes.

11 A If you space throughout 28 days.

12 Q And that this GSH and NAPQI, two-part

13 mechanism that you're talking about here,

14 increases the risk of ASD or ADHD development at

15 18.2 grams spread out 28 times at 650 milligrams a

16 dose. Is that your opinion?

17 MR. ADAMS: Object to form.

18 THE WITNESS: I think you -- you're sort

19 of like limiting it. It could be 18.2 milligrams,

20 even 325 milligrams, you know, over -- over 28

21 days or more.

22 BY MR. PADGETT:

23 Q As long as it's 28 days, your view is

24 it's an increased risk of ASD or ADHD; is that

25 right?

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1 MR. ADAMS: Object to form.

2 BY MR. PADGETT:

3 Q Is that your opinion?

4 A It's written here --

5 Q 28 days or more.

6 MR. ADAMS: Object to form.

7 THE WITNESS: It's my opinion here for

8 at least 28 days during pregnancy, that that was

9 my opinion.

10 BY MR. PADGETT:

11 Q Let's go to pages -- jumping ahead to

12 pages 23 and 24 of your report, Dr. Louie.

13 A 23 or 24?

14 Q It's 23 and 24. You state there that

15 you first reviewed epi studies providing data on

16 days of exposure, and provide a list of the

17 studies -- those particular studies.

18 And then you state that based on review

19 of those studies, quote: I determined that

20 prenatal exposure to acetaminophen in the

21 therapeutic range for at least 28 days increases

22 the risk of developing ASD/ADHD.

23 Did I read that right?

24 A This is on -- going to 25? On the

25 bottom of 24 going to 25?

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1 Q Yes.

2 A I want to make sure -- that's what I

3 wrote.

4 Q Okay. Dr. Louie, I'm going to hand you

5 what's been marked as -- there on page 23 to 24

6 you list various studies, right?

7 A That's correct.

8 (Exhibit No. 24 was marked for

9 identification.)

10 BY MR. PADGETT:

11 Q I'm going to hand you what's been marked

12 as Exhibit 24. Is that the Brandlistuen 2013

13 study referenced there?

14 A That's what -- it's written here, yes.

15 (Exhibit No. 25 was marked for

16 identification.)

17 BY MR. PADGETT:

18 Q I'm also going to hand you what's been

19 marked as Exhibit 25, and is this the Vlenterie

20 study referenced there on page 24 of your report?

21 A It's just two -- right.

22 MR. ADAMS: They've given you 24 and 25.

23 That's 25, that's 24.

24 THE WITNESS: Okay.

25 MR. ADAMS: Is this one 26? It's the

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1 Liew.

2 MR. PADGETT: Liew? Let's see, we have

3 24 is Brandlistuen, correct? 25 is Vlenterie,

4 correct?

5 MS. KAPKE: 26 is Ystrom.

6 (Exhibit No. 26 was marked for

7 identification.)

8 BY MR. PADGETT:

9 Q Is Exhibit 25 the Vlenterie 2016 study,

10 Dr. Louie?

11 A Yes.

12 Q Okay. And is Exhibit 26 the Ystrom 2017

13 study?

14 A It says 2017.

15 Q Ystrom 2017, yeah.

16 A You said 2016.

17 Q Is that Exhibit 26?

18 A That's correct.

19 (Exhibit No. 27 was marked for

20 identification.)

21 BY MR. PADGETT:

22 Q I'm going to hand you what's been marked

23 as Exhibit 27. Is that the Liew 2014 study?

24 A Liew --

25 MR. ADAMS: I don't have 26 or 27, so

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1 the Ystrom and Liew.

2 (Exhibit No. 28 was marked for

3 identification.)

4 BY MR. PADGETT:

5 Q Dr. Louie, I'm going to hand you what's

6 been marked as Exhibit 28, and can you confirm

7 that that is the Liew 2016 study?

8 A Okay. Yes, 28 is Liew 2016.

9 (Exhibit No. 29 was marked for

10 identification.)

11 BY MR. PADGETT:

12 Q And I'm going to hand you what's been

13 marked as Exhibit 29. Is that the Gustavson 2021

14 study referenced there in your report?

15 A '21, right? 2021?

16 Q Yes. It's Exhibit 29, correct?

17 A Correct.

18 Q If you could turn to paragraph 71 to 72

19 of your report.

20 A You said paragraph. Sorry.

21 Q Are you talking about Brandlistuen

22 there?

23 A Yes.

24 Q Okay. Are you there?

25 A Yes.

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1 Q Okay. And there you state that you

2 assign the greatest weight to Brandlistuen 2013

3 because it employed the strongest study design.

4 Right?

5 A Yes.

6 Q And Brandlistuen included a sibling

7 control study with, quote, 2,919 same sibling

8 pairs which allowed them to just for familial and

9 genetic factors, correct?

10 A You mean in paragraph 72, right?

11 Q Yes.

12 A Sorry, because you jumped.

13 Q Is that -- is that correct?

14 A Yes.

15 Q Is it just -- as you put it here, quote,

16 adjusting for familial and genetic factors, a key

17 strength of sibling control studies?

18 A That's -- it helps. It's -- it's both

19 genetic and environmental.

20 Q It makes the study stronger. You agree?

21 A It minimizes variations.

22 Q Okay. Is the use of a sibling control

23 study or analysis part of the reason that you gave

24 the greatest weight to Brandlistuen?

25 MR. ADAMS: Object to form.

<p>Page 114</p> <p>1 THE WITNESS: That's correct.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q Do you agree that not adjusting for</p> <p>4 residual confounding for familial and genetic</p> <p>5 factors is a shortcoming of epidemiology studies</p> <p>6 that do not include sibling control studies, all</p> <p>7 experimental design being the same?</p> <p>8 MR. ADAMS: Object to form.</p> <p>9 THE WITNESS: You're going to have to</p> <p>10 say that again. Slow down. Sorry.</p> <p>11 BY MR. PADGETT:</p> <p>12 Q Is not adjusting for residual</p> <p>13 confounding from familial and genetic factors a</p> <p>14 shortcoming of epidemiology studies that do not</p> <p>15 include sibling control analysis?</p> <p>16 MR. ADAMS: Object to form.</p> <p>17 MR. PADGETT: Strike that.</p> <p>18 BY MR. PADGETT:</p> <p>19 Q Let me put it this way: Do you agree</p> <p>20 that assuming all other study designs are the</p> <p>21 same, you assign greater weight to an epidemiology</p> <p>22 study that does a well done sibling control</p> <p>23 analysis compared to one that does not use a</p> <p>24 sibling control analysis?</p> <p>25 A That's correct.</p>	<p>Page 116</p> <p>1 received or did not receive prenatal acetaminophen</p> <p>2 or compared regarding the risk of ADHD diagnosis,</p> <p>3 end quote.</p> <p>4 Did I read that right?</p> <p>5 A You did.</p> <p>6 Q Do you agree that Gustavson's use of --</p> <p>7 the strong study design that you describe for</p> <p>8 Gustavson includes its use of sibling control</p> <p>9 analysis?</p> <p>10 A They did.</p> <p>11 Q Do you agree that that was part of the</p> <p>12 strength of the study design in Gustavson 2021 was</p> <p>13 its use of a sibling control analysis?</p> <p>14 A As long as they are able to have enough</p> <p>15 patients to give it -- to assess the effects.</p> <p>16 Q And if you could turn to Exhibit 29,</p> <p>17 which is Gustavson 2021.</p> <p>18 MR. PADGETT: Supplemental?</p> <p>19 MS. KAPKE: Yeah.</p> <p>20 BY MR. PADGETT:</p> <p>21 Q Did you read the supplemental materials</p> <p>22 in -- in Gustavson 2021?</p> <p>23 A Did I read it? I may have considered</p> <p>24 it. I don't recollect.</p> <p>25 Q You don't recollect if you --</p>
<p>Page 115</p> <p>1 Q Okay. What do you mean by "assign the</p> <p>2 greatest weight"?</p> <p>3 A I think I said this earlier, that</p> <p>4 there's a hierarchical -- that means more</p> <p>5 confidence in the data that -- that's coming out.</p> <p>6 Q And assuming all experimental designs</p> <p>7 design for two studies the same, looking at the</p> <p>8 same endpoints, would you give greater weight to</p> <p>9 the one that used sibling control analysis?</p> <p>10 MR. ADAMS: Object to form.</p> <p>11 THE WITNESS: In the context that they</p> <p>12 have the same number of patients, I think that's a</p> <p>13 better design.</p> <p>14 BY MR. PADGETT:</p> <p>15 Q Okay. Fast-forward to paragraph 78,</p> <p>16 please.</p> <p>17 And there again -- and you're talking</p> <p>18 about the Gustavson 2021 study, right?</p> <p>19 A 78?</p> <p>20 Q Yes.</p> <p>21 A Okay. Start -- okay, yes.</p> <p>22 Q And there you say that you, quote, gave</p> <p>23 weight to, end quote, Gustavson 2021, quote, based</p> <p>24 on its strong study design, end quote, and you</p> <p>25 notice comparison of siblings whose mothers either</p>	<p>Page 117</p> <p>1 A Yeah.</p> <p>2 Q -- reviewed the supplemental materials.</p> <p>3 A Yeah.</p> <p>4 Q Okay.</p> <p>5 (Exhibit No. 30 was marked for</p> <p>6 identification.)</p> <p>7 BY MR. PADGETT:</p> <p>8 Q Okay. I'm going to hand you what's been</p> <p>9 marked as Exhibit 30 and --</p> <p>10 A Can I put this down?</p> <p>11 Q Yeah, we'll be coming back to it.</p> <p>12 Do you recognize Exhibit 30 as the</p> <p>13 supplemental materials for Gustavson 2021?</p> <p>14 MR. ADAMS: I'm not sure what's going</p> <p>15 on.</p> <p>16 MS. KAPKE: There's two copies there.</p> <p>17 MR. PADGETT: Sorry. Apologies.</p> <p>18 THE WITNESS: I'm sorry. I didn't know.</p> <p>19 BY MR. PADGETT:</p> <p>20 Q First of all, do you recall reviewing</p> <p>21 those materials?</p> <p>22 A (Peruses document.)</p> <p>23 Q Do they look familiar, I guess is my</p> <p>24 question?</p> <p>25 A Not really.</p>

<p style="text-align: right;">Page 118</p> <p>1 Q Okay.</p> <p>2 A So let me -- give me a few moments.</p> <p>3 (Peruses document.) Okay.</p> <p>4 Q Have you reviewed that sufficiently to</p> <p>5 determine whether you reviewed the supplemental</p> <p>6 materials for Gustavson 2021 before signing your</p> <p>7 report, or ever?</p> <p>8 A It's not familiar.</p> <p>9 Q Okay. In paragraph 78 of your report,</p> <p>10 you state that: "The adjusted hazard ratio from</p> <p>11 Gustavson 2021 for mothers who use acetaminophen</p> <p>12 for 29 days or more was 2.02." Is that correct?</p> <p>13 A I believe this is coming straight from</p> <p>14 the paper.</p> <p>15 Q Straight from the paper. Let's go to</p> <p>16 the paper, page 7, Table 2.</p> <p>17 Are you there?</p> <p>18 A Yeah, I just got there.</p> <p>19 Q Okay. The -- is that number that you</p> <p>20 put in there in paragraph 78, the 2.02 for the</p> <p>21 risk of ADHD in children whose mothers used</p> <p>22 acetaminophen 29 days or more, is that the sibling</p> <p>23 control analysis adjusted hazard ratio?</p> <p>24 A No, it's the long-term exposure, 29 or</p> <p>25 more days associated with a twofold increase in</p>	<p style="text-align: right;">Page 120</p> <p>1 issues of this evaluation.</p> <p>2 Q Dr. Louie, you didn't put the</p> <p>3 nonstatistically significant sibling control</p> <p>4 analysis adjusted HR in your report, did you?</p> <p>5 A I did -- I did not do it for that, but</p> <p>6 neither did I do it for the model 3 where it's</p> <p>7 2.77, right. And so I don't think I put that as</p> <p>8 well.</p> <p>9 Q What are you talking about 2.77?</p> <p>10 A Page 7, all the way to the bottom, the</p> <p>11 corner, "Family effect for model 3," you have a</p> <p>12 hazard ratio of 2.77. I didn't -- I didn't</p> <p>13 mention that as well in my report.</p> <p>14 Q Okay. And what -- what is your</p> <p>15 understanding of the family effect number?</p> <p>16 A Well, my understanding just from looking</p> <p>17 at this data is that this is statistically</p> <p>18 significant, and it's a 2.77-fold increase, and</p> <p>19 it's statistically significant.</p> <p>20 Q Your understanding is that 2.77 isn't a</p> <p>21 number reflecting the familial effect due to the</p> <p>22 analysis -- of the sibling control analysis that</p> <p>23 they did?</p> <p>24 A I'm suggesting to you I didn't put --</p> <p>25 for one, I didn't put one that's negative, nor did</p>
<p style="text-align: right;">Page 119</p> <p>1 ADHD diagnosis. So, no.</p> <p>2 Q It wasn't the sibling control analysis,</p> <p>3 right?</p> <p>4 A No, at least -- yes.</p> <p>5 Q And in Table 2, that's model 2.</p> <p>6 Model 3 is adjusted and controlled for</p> <p>7 family effect. That -- those are the numbers for</p> <p>8 the sibling control analysis, right?</p> <p>9 A Model 2?</p> <p>10 Q Model 3.</p> <p>11 A Oh, sorry. Uh-huh. Yes.</p> <p>12 Q Based on Gustavson 2021, that</p> <p>13 pre-sibling control analysis adjusted hazard ratio</p> <p>14 of 2.02 for more than -- for 29 days or more of</p> <p>15 use was attenuated down to the null when they did</p> <p>16 a sibling control analysis, correct?</p> <p>17 A What you do you mean by "null"?</p> <p>18 Q It was attenuated down to 1.06 and not</p> <p>19 statistically significant, correct?</p> <p>20 A It's not statistically significant, but</p> <p>21 it's not null. So therefore, I think what you</p> <p>22 need to be -- I think the number of patients in</p> <p>23 this -- I don't know where I read it, but it was</p> <p>24 the number of patients that were evaluated were</p> <p>25 relatively low. So that's -- it was one of the</p>	<p style="text-align: right;">Page 121</p> <p>1 I put one for the positive as well. So I didn't</p> <p>2 address that point.</p> <p>3 Q Okay. What are you saying that the 2.77</p> <p>4 number is about?</p> <p>5 A Well, it shows that it's -- I'm just</p> <p>6 showing you the relationships, that if you were to</p> <p>7 look at all the other on day 29, if you look at</p> <p>8 model 1, model 2, model 3, model 4, you pick the</p> <p>9 one that didn't have it -- have statistical</p> <p>10 significance, whereas all the other ones were all</p> <p>11 statistically significant.</p> <p>12 Q What -- can you turn to page 5 of the</p> <p>13 report.</p> <p>14 MR. ADAMS: The study or the report?</p> <p>15 MR. PADGETT: Of the -- sorry, of the</p> <p>16 study.</p> <p>17 THE WITNESS: Of the study. Okay.</p> <p>18 BY MR. PADGETT:</p> <p>19 Q And do you see there under "Results,"</p> <p>20 the paragraph that starts "Exposure," the fourth</p> <p>21 paragraph there?</p> <p>22 A I'm there.</p> <p>23 Q Okay. And the sentence that starts "All</p> <p>24 children"?</p> <p>25 A "All children." Okay.</p>

<p style="text-align: right;">Page 122</p> <p>1 Q Can you read that sentence for me.</p> <p>2 A "All children, both exposed and</p> <p>3 unexposed, born to a mother with long-term use of</p> <p>4 acetaminophen in one pregnancy had increased risk</p> <p>5 of receiving a -- an ADHD diagnosis compared to</p> <p>6 children of a mother who did not use acetaminophen</p> <p>7 in any pregnancy."</p> <p>8 Q So do you have a better understanding of</p> <p>9 what that 2.77 number is in Table 2?</p> <p>10 A I do.</p> <p>11 Q Okay. What is it?</p> <p>12 A They looked at it compared to both</p> <p>13 exposed and unexposed born to a mother with</p> <p>14 long-term use.</p> <p>15 Q So long-term use for unexposed siblings</p> <p>16 has showed a significant family effect for</p> <p>17 subsequent ADHD clinical diagnosis, correct?</p> <p>18 A That's what it states here.</p> <p>19 Q Okay. Are you questioning the</p> <p>20 conclusion made in Gustavson 2021?</p> <p>21 A No.</p> <p>22 Q Okay. So you pointed this out, what</p> <p>23 that family effect for model 3 on Table 2 shows is</p> <p>24 a statistically significant familial effect shown</p> <p>25 by the sibling control analysis, right?</p>	<p style="text-align: right;">Page 124</p> <p>1 adjusted HR in Gustavson 2021 before the sibling-</p> <p>2 control analysis did not show an increased risk,</p> <p>3 right, looking at Table 2?</p> <p>4 A I'm sorry, I closed it already.</p> <p>5 Table 2. Go ahead.</p> <p>6 And which model are you referring to?</p> <p>7 Q Model 2.</p> <p>8 A Model 2.</p> <p>9 Q Pre-sibling control analysis. Neither 1</p> <p>10 to 7 days or days 8 to 28 days showed any</p> <p>11 statistically significant association.</p> <p>12 A In this study, that's what it said.</p> <p>13 Q Eight to 28 days of finding no</p> <p>14 association is inconsistent with your opinion in</p> <p>15 this case that exposure for at least 28 days leads</p> <p>16 to an increased risk of ADHD or ASD, right?</p> <p>17 A Fair, Counsel, yeah, that's -- and</p> <p>18 that's why if you look at it, it's 1.13. That</p> <p>19 means the hazard ratio did go up compared to the</p> <p>20 reference 0.87. Then you looked at 29 days, just</p> <p>21 one extra day, and guess what, it goes down to</p> <p>22 2.0. So therefore, it shows you exposure effects.</p> <p>23 Q And the sibling control analysis showed</p> <p>24 no association for 29 days more, right -- or more,</p> <p>25 right?</p>
<p style="text-align: right;">Page 123</p> <p>1 A Yes.</p> <p>2 Q Okay. I know the Gustavson 2021 uses</p> <p>3 the threshold -- or uses -- I mean, your 2.02</p> <p>4 number, which was a pre-sibling control analysis,</p> <p>5 is for 29 days or more, right?</p> <p>6 A That's what the bucket says in this</p> <p>7 paragraph, yeah.</p> <p>8 Q Okay. So technically, even that number,</p> <p>9 pre-sibling control analysis is not consistent</p> <p>10 with your 28 days threshold, right?</p> <p>11 MR. ADAMS: Object to form.</p> <p>12 THE WITNESS: No, I -- I said it was 28</p> <p>13 days or more.</p> <p>14 BY MR. PADGETT:</p> <p>15 Q But Gustavson would be 29 days or more,</p> <p>16 right?</p> <p>17 MR. ADAMS: Object to form.</p> <p>18 THE WITNESS: I took that into</p> <p>19 consideration, but if you look at my opinion, it</p> <p>20 was 28 days and more.</p> <p>21 BY MR. PADGETT:</p> <p>22 Q Okay.</p> <p>23 A So I think 29 days is more than 28 days.</p> <p>24 So...</p> <p>25 Q For exposure of 8 to 28 days, the</p>	<p style="text-align: right;">Page 125</p> <p>1 MR. ADAMS: Object to form.</p> <p>2 THE WITNESS: You -- but if you use</p> <p>3 model 1, it gave that.</p> <p>4 BY MR. PADGETT:</p> <p>5 Q My question is sibling control analysis,</p> <p>6 model 3, 29 days or more, attenuated down to no</p> <p>7 statistically significant association, right?</p> <p>8 A That's what it states here.</p> <p>9 Q When you say, That's what it states</p> <p>10 there, are you questioning the findings here?</p> <p>11 A Well --</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 THE WITNESS: I think the hazard ratio</p> <p>14 here is 1.06. I see that's not statistically</p> <p>15 significant, but there's still -- anything above</p> <p>16 1.0 is considered a risk.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q Even though -- is statistical</p> <p>19 significance important to you in terms of your</p> <p>20 weighing and evaluating these studies?</p> <p>21 A It gives me an idea that there is still</p> <p>22 a signal.</p> <p>23 Q And both 1 to 7 days and 8 to 28 days,</p> <p>24 model 3, the sibling control analysis showed an</p> <p>25 attenuation down to below 1.0 for both, right?</p>

<p style="text-align: right;">Page 126</p> <p>1 A Say that again.</p> <p>2 Q One to 7 and 8 to 28 days, the sibling</p> <p>3 control analysis showed an attenuation of the risk</p> <p>4 down to below 1.0, right?</p> <p>5 A On the 8 to 28 days. But you need to</p> <p>6 also --</p> <p>7 Q And 1 to 7 days, right?</p> <p>8 A And that's the reference. So therefore,</p> <p>9 it shows you that this group was -- was less,</p> <p>10 yeah.</p> <p>11 Q Okay. You indicated that even though</p> <p>12 it's not statistically significant, something</p> <p>13 above 1.0 shows risk. Is that -- was that your</p> <p>14 testimony?</p> <p>15 A That's normally how it -- well, that is</p> <p>16 how hazard ratios shows something. Anything above</p> <p>17 1.0 is a risk.</p> <p>18 Q Okay. So you note -- do you see that</p> <p>19 for 1 to 7 days, the sibling control analysis</p> <p>20 attenuated the pre-sibling control AR -- AHR down</p> <p>21 to below 1.0? Do you see that?</p> <p>22 A So --</p> <p>23 Q 0.75, right?</p> <p>24 A 0.75, yes.</p> <p>25 Q Okay. And that's -- the confidence</p>	<p style="text-align: right;">Page 128</p> <p>1 BY MR. PADGETT:</p> <p>2 Q You said, "It does not"?</p> <p>3 A Does not. I mean, reach a null -- it</p> <p>4 reach a null, right? It's the null hypothesis</p> <p>5 that it reached.</p> <p>6 Q It reached a null hypothesis.</p> <p>7 A Right.</p> <p>8 Q If it had been 0.99, would you agree</p> <p>9 that that's -- would have been suggestive of an</p> <p>10 inverse correlation in terms of risk, a protective</p> <p>11 effect?</p> <p>12 A I don't think I could do that.</p> <p>13 Q Okay. Have you reviewed sibling control</p> <p>14 studies for other proposed risk factors for ASD or</p> <p>15 ADHD to compare adjusted hazard ratios?</p> <p>16 MR. ADAMS: Object to form.</p> <p>17 THE WITNESS: Are you talking about this</p> <p>18 case or are you talking about something else?</p> <p>19 BY MR. PADGETT:</p> <p>20 Q I'm talking about something else.</p> <p>21 Have you reviewed sibling control</p> <p>22 studies on other proposed risk factors for ASD or</p> <p>23 ADHD to look at the associations adjusted hazard</p> <p>24 ratios?</p> <p>25 A So you asked me several questions, and</p>
<p style="text-align: right;">Page 127</p> <p>1 interval there is nearly a statistically</p> <p>2 significant inverse association.</p> <p>3 Do you agree?</p> <p>4 A How do you calculate that?</p> <p>5 Q Because the confidence interval is 0.56</p> <p>6 to 1.03.</p> <p>7 A It crosses 1.0.</p> <p>8 Q It crosses 1.0, right. So is that</p> <p>9 significant to you that it's not statistically</p> <p>10 significant?</p> <p>11 MR. ADAMS: Object to form.</p> <p>12 THE WITNESS: I'm not going to battle</p> <p>13 with you on terms because I don't have the data in</p> <p>14 front of me, I mean in terms of the raw data, how</p> <p>15 it was adjusted, but I would tell you -- I'm not</p> <p>16 sure I understand your question.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q So you pointed to 1.06 for 20 -- more</p> <p>19 than 29 days or more as -- as an increased risk,</p> <p>20 even though it's not statistically significant,</p> <p>21 right? But when asked if 0.75 with a top end</p> <p>22 confidence interval of 1.03, statistical</p> <p>23 significance matters there?</p> <p>24 MR. ADAMS: Object to form.</p> <p>25 THE WITNESS: It does not.</p>	<p style="text-align: right;">Page 129</p> <p>1 then you narrowed it down to only ADS -- ASD and</p> <p>2 ADHD, correct?</p> <p>3 Q Right.</p> <p>4 A No, not for -- for those.</p> <p>5 Q And so you've not looked at whether</p> <p>6 other -- so you don't know whether studies on</p> <p>7 labor induction has -- in relationship with ASD or</p> <p>8 ADHD showed sibling control analysis similarly</p> <p>9 attenuating adjusted hazard ratios down to the</p> <p>10 null as Gustavson did?</p> <p>11 MR. ADAMS: Object to form.</p> <p>12 THE WITNESS: I didn't review that.</p> <p>13 BY MR. PADGETT:</p> <p>14 Q Okay. You just reviewed these two</p> <p>15 sibling control analysis studies on ADHD, right?</p> <p>16 MR. ADAMS: Object to form.</p> <p>17 THE WITNESS: Are you asking me if I</p> <p>18 only did sibling controls just for ADHD and ASD,</p> <p>19 but you didn't ask me --</p> <p>20 BY MR. PADGETT:</p> <p>21 Q Acetaminophen.</p> <p>22 A -- other things, right? Okay. No, I</p> <p>23 haven't.</p> <p>24 Q Okay. If you go back to page 7 of</p> <p>25 Gustavson, right column, second paragraph.</p>

<p style="text-align: right;">Page 130</p> <p>1 There it states on the right starting</p> <p>2 with the word "Different" -- or sorry, starting</p> <p>3 with "The previous study."</p> <p>4 Quote: A previous study using the MoBa</p> <p>5 cohort found an association between maternal</p> <p>6 acetaminophen use during pregnancy and mother</p> <p>7 reported symptoms of externalizing symptoms when</p> <p>8 the children were born -- were three years old,</p> <p>9 and cites Brandlistuen 2013. Different results in</p> <p>10 a current study may be due to the use of ADHD</p> <p>11 diagnoses rather than maternal report of symptoms</p> <p>12 or that children in the previous study were only</p> <p>13 three years old, end quote.</p> <p>14 Did I read that correctly?</p> <p>15 A You -- can you tell me where exactly on</p> <p>16 page 7 again?</p> <p>17 Q It's the paragraph that says "A previous</p> <p>18 study."</p> <p>19 A Previous study. Oh, "A previous study."</p> <p>20 Q Yes.</p> <p>21 A Okay. I was looking for "the." Sorry.</p> <p>22 (Peruses document.)</p> <p>23 Q Have you read it?</p> <p>24 A Yes.</p> <p>25 Q Okay. Basically it says -- Gustavson</p>	<p style="text-align: right;">Page 132</p> <p>1 to last sentence.</p> <p>2 A "However, because clinical</p> <p>3 assessment" --</p> <p>4 MR. ADAMS: One second. Do you want him</p> <p>5 to read it out loud or to himself?</p> <p>6 BY MR. PADGETT:</p> <p>7 Q Go ahead and read it to yourself. Did</p> <p>8 you read it?</p> <p>9 A No, I haven't.</p> <p>10 Q Okay, go ahead.</p> <p>11 A (Peruses document.) Yes.</p> <p>12 Q So with regard to clinical diagnosis</p> <p>13 versus screening tools, Brandlistuen authors state</p> <p>14 that, quote: Because clinical assessments with</p> <p>15 diagnostic tools were not available in this study,</p> <p>16 we could not determine the clinical importance of</p> <p>17 the differences observed. Future studies should</p> <p>18 seek to include clinical diagnoses of</p> <p>19 neurodevelopmental and behavioral diagnoses to</p> <p>20 explore whether there was an increased risk of,</p> <p>21 for example, attention-deficit/hyperactivity</p> <p>22 disorder or language disorders after exposure to</p> <p>23 long-term paracetamol used during pregnancy.</p> <p>24 Did I read that correctly?</p> <p>25 A You did.</p>
<p style="text-align: right;">Page 131</p> <p>1 2021 points to Brandlistuen as a previous study</p> <p>2 that reported an association between maternal</p> <p>3 acetaminophen use in pregnancy and mother reported</p> <p>4 symptoms -- externalizing symptoms when they were</p> <p>5 three years old.</p> <p>6 And it -- Gustavson says: "Different</p> <p>7 results in the current study may be due to the use</p> <p>8 of ADHD diagnoses rather than maternal report of</p> <p>9 symptoms." Right?</p> <p>10 A That's what they said.</p> <p>11 Q Or that the children were only three</p> <p>12 years old, right?</p> <p>13 A Right. And if you were to look further</p> <p>14 on, you would see that as well.</p> <p>15 Q Brandlistuen -- the Brandlistuen 2013</p> <p>16 study did not use ASD or ADHD diagnoses, right?</p> <p>17 A No, it didn't.</p> <p>18 Q Okay. If you could turn to</p> <p>19 Brandlistuen, Exhibit 24, please.</p> <p>20 And what I'd like you to do is turn to</p> <p>21 page 1711, the left column, final sentence.</p> <p>22 Can you read that, please.</p> <p>23 A Where are you --</p> <p>24 Q Page 1711, the left column. And that</p> <p>25 final sentence starting with "However." Or second</p>	<p style="text-align: right;">Page 133</p> <p>1 Q Okay. Do you agree with the authors</p> <p>2 there?</p> <p>3 A I agree with the authors. They actually</p> <p>4 published additional papers verifying their</p> <p>5 findings that there was an increased risk.</p> <p>6 Q Pre-sibling control analysis, right?</p> <p>7 A Even if it's not pre-sibling analysis,</p> <p>8 there's several studies that shows that, right?</p> <p>9 Q Gustavson '21 -- 2021 focused</p> <p>10 specifically on clinical diagnosis -- diagnoses of</p> <p>11 ADHD as the Brandlistuen authors suggested doing</p> <p>12 here, right?</p> <p>13 A Correct.</p> <p>14 Q Okay. After discussion of Brandlistuen</p> <p>15 2013, paragraph 74, you discuss the Ystrom study,</p> <p>16 which is Exhibit 26.</p> <p>17 And paragraph 74 of your report, you</p> <p>18 note that Ystrom found association with</p> <p>19 acetaminophen use for more than 29 days, right?</p> <p>20 A In my report or in the --</p> <p>21 Q In your report.</p> <p>22 A Okay, where are we?</p> <p>23 Q Paragraph 74.</p> <p>24 A (Peruses document.)</p> <p>25 Q Do you see that?</p>

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1 A Okay, yeah.

2 Q Okay. Taking away this study does not

3 support your threshold of 28 days -- cumulative

4 days of exposure for increased risk, correct?

5 MR. ADAMS: Object to form.

6 THE WITNESS: Can you say that again?

7 BY MR. PADGETT:

8 Q Well, let's look at table -- Table 2 on

9 page 4 of the Ystrom study.

10 Does Ystrom show a statistically

11 significant association for ADHD for less than or

12 equal to 9 days, 8 to 14 days, 15 to 21 days, or

13 28 to 29 --

14 A One at a time.

15 MR. ADAMS: One second. Question.

16 Object to form.

17 BY MR. PADGETT:

18 Q Does Ystrom show any statistically

19 significant association below 29 days?

20 MR. ADAMS: Object to form.

21 THE WITNESS: So if you looked at your

22 Table 2, 15 to 21 days use, you get statistical

23 significance. So...

24 BY MR. PADGETT:

25 Q It includes 1.0. If it includes 1.0,

Page 135

1 that's not statistically --

2 A Okay.

3 Q -- significant, correct? Agree?

4 A Okay, that's fine. That's right on the

5 borderline.

6 Q So there's no statistically significant

7 finding in Ystrom for anything below 29 days.

8 Agree?

9 A Agree. But if you were to look at the

10 fevers -- see, you go -- scroll to the right-hand

11 side, those adjusted for fevers and infection, you

12 have statistical significance, and the hazard

13 ratio is 6.0.

14 Q And that's a very large confidence

15 interval, wouldn't you agree?

16 A Still statistically significant, as you

17 like to pose it, right.

18 Q If you could turn to page 2 of Ystrom.

19 The middle -- the middle column.

20 The authors reported using paternal use

21 before pregnancy as part of their analysis, right?

22 A Where are you? I'm in the middle, but

23 which paragraph?

24 Q Strike that.

25 If you could look at Table 3. On

Page 136

1 page 7.

2 Do you see that Ystrom showed

3 statistically significant associations with

4 offspring with subsequent ADHD diagnosis for

5 paternal use of acetaminophen six months before

6 pregnancy? Do you see that? At least for 8 to 28

7 days or 29 days or more?

8 A I see that.

9 Q Okay. Given that the results are based

10 on paternal use and six months prior to pregnancy,

11 do you agree that that's indicative of residual

12 confounding that may be present?

13 A So paternal is father, right?

14 Q Yes.

15 A So you're saying -- at least from this

16 analysis is saying that acetaminophen affects the

17 father to cause this issue.

18 Q The father isn't carrying the baby,

19 correct?

20 A The father has the sperm.

21 Q Okay. Are you saying that there's some

22 type of effect on sperm, a genetic effect that is

23 resulting --

24 MR. ADAMS: Object to form.

25 BY MR. PADGETT:

Page 137

1 Q -- in this association?

2 MR. ADAMS: Object to form.

3 THE WITNESS: Well, you're telling me

4 that there's a confounding issue. Acetaminophen

5 is causing an issue here. That's what you're

6 saying, right?

7 BY MR. PADGETT:

8 Q No, I'm saying that isn't this

9 indicative of a genetic confounding factor

10 involving the father's contribution in increased

11 use of acetaminophen?

12 MR. ADAMS: Object to form.

13 THE WITNESS: This says paternal

14 acetaminophen use. It didn't talk about genetics.

15 BY MR. PADGETT:

16 Q How can paternal use be associated with

17 an increased risk of ADHD in subsequent offspring

18 used six months before pregnancy?

19 MR. ADAMS: Object to form.

20 THE WITNESS: Counsel, you -- you

21 brought this up, and so therefore, it says -- it

22 doesn't say paternal genetics. It's paternal use.

23 So, I mean, to me, to be honest with

24 you, you brought that up, and it shows that there

25 is some hazard ratios. What does that mean?

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1 BY MR. PADGETT:

2 Q Are you aware of any study on sperm and

3 genetic or epigenetic changes tied to ASD or ADHD?

4 A I'm not even -- that was not part of my

5 assignment. I didn't look at that.

6 Q So your answer is "no."

7 MR. ADAMS: Object to form. Let him

8 finish his answer.

9 THE WITNESS: You answered for me, and

10 the answer is no, but -- since you answered for

11 me, let me explain. I didn't bring this issue up,

12 you did. So to me when you interpret it that way,

13 I think you misinterpreted.

14 BY MR. PADGETT:

15 Q Do you -- so you're saying that this

16 cannot be interpreted as genetic confounding?

17 MR. ADAMS: Object to form.

18 THE WITNESS: The table doesn't say

19 genetics. So -- it says acetaminophen use. So

20 I'm trying to understand what you're trying to ask

21 me.

22 BY MR. PADGETT:

23 Q Could you turn to Exhibit 27, please.

24 It should be Liew 2014.

25 A Can I close this out?

Page 139

1 Q Yes.

2 A Sorry, was it 27?

3 Q Yes. Liew 2014.

4 Are you familiar with this study?

5 A I believe it's in my report.

6 Q Okay. And in Liew 2014, acetaminophen

7 use was ascertained through interviews during

8 pregnancy, right?

9 A That's the study design.

10 Q And do you agree that maternal reporting

11 of acetaminophen use can suffer from reporting

12 bias?

13 A Say what you said again.

14 Q Do you agree that maternal reporting of

15 acetaminophen use in a study like this can suffer

16 from reporting bias?

17 A It could.

18 Q Okay. And if you turn to page 319, the

19 left column, the second to last sentence.

20 A 319.

21 Q And if you could read that sentence at

22 the end -- towards the end of the paragraph with

23 "We were unable to assess." Do you see that?

24 A 319, which --

25 Q Left-hand column.

Page 140

1 A Okay.

2 Q It states they were unable to assess the

3 influence of dosage or number of pills taken

4 because the mothers were unable to recall the

5 information accurately.

6 A I'm sorry, paragraph 1 or paragraph 2?

7 Q Paragraph -- the end of that left-hand

8 column, starting with "We were unable to assess."

9 Do you see that?

10 MR. ADAMS: As he is reading, I've got

11 two copies of Liew 2016.

12 THE REPORTER: I didn't get one.

13 MR. ADAMS: Do you need one of these?

14 THE REPORTER: Yes.

15 BY MR. PADGETT:

16 Q Have you read that, Dr. Louie?

17 A This is the one, right, because it looks

18 different. I'm scared now.

19 MR. ADAMS: One second. I need a copy

20 of that exhibit.

21 MS. KAPKE: Which one, Liew 2014?

22 MR. ADAMS: Yes. I got two copies of

23 the 2016 one and --

24 BY MR. PADGETT:

25 Q Do you have 2014? Are you looking at

Page 141

1 Liew 2014?

2 A Oh, I'm looking at Liew 2014.

3 Q Yes.

4 A Is that the right one?

5 Q That's the right one.

6 A Okay.

7 Q If you look at page 319, the left-hand

8 column, have you read that language, "We were

9 unable to assess"?

10 A Yes. About 28 percent of the mothers

11 who reported acetaminophen use...

12 Yeah.

13 Q Well, they couldn't -- they were unable

14 to specify the gestational week, right?

15 A Correct.

16 Q And they were unable to assess -- the

17 author said they were unable to assess the

18 influence of dosage or number of pills taken

19 because the mothers couldn't -- were unable to

20 recall that information accurately, right?

21 A Correct, that's what it says here.

22 Q And do you know whether the authors in

23 Liew 2014 were able to assess residual confounding

24 due to familial and genetic factors?

25 A Where are you referring to?

Page 142

1 Q I'm just asking if you know whether they
2 were able to assess familial and genetic factors.
3 MR. ADAMS: Object to form.
4 THE WITNESS: You're going to have to
5 point me to that because I don't remember it.
6 BY MR. PADGETT:
7 Q Did they make any -- do you know if they
8 made any attempt to assess familial or genetic
9 confounding factors in Liew 2014?
10 MR. ADAMS: Object to form.
11 THE WITNESS: We have the paper here.
12 If you could point me to it, then I could see it.
13 BY MR. PADGETT:
14 Q It may not be in there, but my question
15 is, do you know whether they did that?
16 A Well, unfortunately, I don't remember
17 everything I read.
18 Q Okay.
19 A So I don't recall.
20 Q Can you turn to Liew 2016, which is
21 Exhibit 28.
22 A Can I put 27 down?
23 Q Yes.
24 A Is it this one?
25 Q Yes.

Page 143

1 A Okay.
2 Q In your report you reference that there
3 was an increased HR for exposure to acetaminophen
4 during two to five weeks -- two to five weeks of
5 an increased risk of ASD in offspring.
6 A Can you tell me in the report where I
7 said that?
8 Q Let's just turn to Table 2 of Liew 2016.
9 A Okay. Okay. (Peruses document.)
10 Q Do you see that the adjusted HR is 1.23
11 for two to five weeks down there at the bottom in
12 the middle adjusted HR?
13 A Mm-hmm.
14 Q Do you see that?
15 A Yes.
16 Q Okay. And then 6 to 20 weeks is not
17 statistically significant and no association.
18 Agree?
19 A That's what it says. And the number of
20 cases went almost right in half.
21 Q Okay. Would you agree that that is
22 inconsistent with a dose-response relationship in
23 this study?
24 A I don't --
25 MR. ADAMS: Object to form.

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1 THE WITNESS: I do not because the
2 number of cases dropped. So therefore, if you had
3 159 cases, would you get that?
4 BY MR. PADGETT:
5 Q Well, as you pointed out earlier, the
6 confidence interval is still not statistically
7 significant for 81 cases, right?
8 A That's correct, but if you -- when you
9 make a comment like that, you have to -- if you
10 gave it enough effect size, would it come back up?
11 Q That's speculation. Agree?
12 MR. ADAMS: One second. One second.
13 Question?
14 BY MR. PADGETT:
15 Q That's speculation, do you agree?
16 MR. ADAMS: Object to form.
17 THE WITNESS: Okay. It would be -- to
18 compare things, because you make me want to
19 conclude, and I say that the only way to conclude
20 is to have enough patients to evaluate that.
21 BY MR. PADGETT:
22 Q Would you turn to Exhibit 28, Liew 2016.
23 Are you still there?
24 A I'm sorry, 20?
25 Q 2016.

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1 MR. ADAMS: Same exhibit.
2 THE WITNESS: Okay. Okay. Which page?
3 BY MR. PADGETT:
4 Q 256.
5 A Liew 216 -- 256?
6 Q Sorry, 956. 956, left column, first
7 paragraph.
8 A Line -- okay.
9 Q Okay. And do you see, "We performed" --
10 the authors state that: "We performed a
11 dose-response analysis by counting total weeks of
12 use. However, exact dosage -- dosages cannot be
13 estimated because more than 80 percent of the
14 interviewed women were unable to recall this
15 information."
16 Do you see that?
17 A Eighty percent -- okay. That's correct.
18 Q Okay. The authors were not able -- the
19 authors were able to collect little data on the
20 actual quantity of exposure in this study, right?
21 MR. ADAMS: Object to form.
22 THE WITNESS: While they may have lacked
23 the data, they show you that the time of exposure
24 did have -- in Table -- Table 3 and Table 2 shows
25 you that there is statistical significance.

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1 Right.

2 Because they -- they -- in the table

3 itself, weeks of acetaminophen use throughout

4 pregnancy. Even though they didn't have the

5 data that you're -- that they're saying, you still

6 see that in the autism disorder group they showed

7 a statistic analysis.

8 BY MR. PADGETT:

9 Q And that statistical significance was

10 only for autism with hyperkinetic disorder, right?

11 A Yes, and -- but do -- well, wait, wait,

12 wait. No, not on top. It doesn't -- it doesn't

13 -- Table 2 doesn't just look at hyperkinetic. It

14 looks at the crude.

15 Q Can you turn to page 954, please.

16 Under "Discussion," right column, end of

17 the second paragraph, could you read starting with

18 the word "If" there at the bottom of that

19 paragraph.

20 A At the bottom -- "if." Okay. Is it "If

21 ASD" -- is that --

22 Q Mm-hmm, yes.

23 A "If ASD in hyperkinetic disorders are

24 considered two different disorders with different

25 etiologies, our results can be interpreted as

Page 147

1 acetaminophen only having an impact in

2 hyperkinetic disorders but not ASD."

3 Q Do you agree with that based on the

4 data?

5 A They said "if," and so therefore, in

6 their crude -- and that's in Table 2 -- it shows

7 you that there is -- there is a statistical

8 significance, even --

9 Q Let me ask you this: Did you consider

10 the finding that ASD was only associated with

11 hyperkinetic disorder accompanying it with regard

12 to your analysis of ASD and the risk?

13 MR. ADAMS: Object to form.

14 THE WITNESS: What I did was I took what

15 the data gave me, and I used the data that they

16 gave me, and I don't try to overinterpret it. The

17 data is what the data says.

18 BY MR. PADGETT:

19 Q Okay.

20 MR. ADAMS: We've been going over an

21 hour. It's 12:37. I don't know if you want to

22 end or you want to continue or -- lunch is here.

23 MR. PADGETT: I can go 10 minutes, and

24 we can -- if that's all right.

25 MR. ADAMS: Are you good?

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1 THE REPORTER: (Reporter nods.)

2 BY MR. PADGETT:

3 Q In Liew 2016, the authors did not

4 control for family -- familial or genetic

5 confounding, right?

6 A Where are you referring to?

7 Q Page 956, left column, last paragraph.

8 A 956 -- last paragraph on the left-hand

9 side?

10 Q Yes.

11 A Okay. (Peruses document.)

12 Q My question is they were not able to

13 exclude the possibility of residual confounding by

14 indication or genetic factors as alternate

15 explanations for their findings, right?

16 A Yeah. So in all these -- in all

17 publications we're always supposed to explain our

18 limitations. So they were being transparent in

19 showing you that there's limitations in every

20 study.

21 Q And the sibling control analysis is

22 geared towards controlling for residual

23 confounding by genetic factors or familial

24 factors, right?

25 A I don't think they -- they used that.

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1 Q If you could turn to the Vlenterie

2 study. It's Exhibit 25.

3 A So can I put this away, or are you going

4 to come back to it?

5 Q Yes. Yes.

6 A You have to let me know if I can put it

7 away because it -- Vlenterie.

8 This one?

9 Q Right. And in your report you reference

10 the communications problems, and there was -- as

11 an association.

12 A Can you -- in my report?

13 Q Paragraph 79 of your report --

14 A Thank you.

15 Q -- you discuss Vlenterie.

16 Do you see that?

17 A Yes.

18 Q And you reference communications as

19 showing an increased risk, right?

20 A There was an odds ratio, yes.

21 Q The odds ratio includes 1.0, right?

22 A Correct.

23 Q And that is not statistically

24 significant, correct?

25 MR. ADAMS: Object to form.

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1 THE WITNESS: And -- and I just show you
 2 what the data says. I'm not trying to hide
 3 anything.
 4 BY MR. PADGETT:
 5 Q Okay. This study doesn't address ASD or
 6 ADHD diagnoses specifically, right?
 7 A They use a, what I think they call,
 8 propensity score, so it is not diagnostic.
 9 Q Okay. The authors assess the impact.
 10 If you look at page 2000, Figure 1.
 11 A Where -- where -- in the -- in the
 12 paper?
 13 Q Yes, in the paper.
 14 A 2001 or 2000?
 15 Q Page 2000.
 16 Figure 1, they looked at -- do you see
 17 where it says "complete cases," and there's a --
 18 the box, it's the various endpoints that they
 19 looked at. Do you see that?
 20 A Yeah, I see that.
 21 Q So they looked at ten different outcomes
 22 in this study, right?
 23 A That's correct.
 24 Q Okay. Did you confirm whether the
 25 authors performed a statistical correction to

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1 address errors that may result from multiple
 2 hypotheses at the same time?
 3 A Can you say that again?
 4 Q Did you confirm whether the Vlenterie
 5 2016 authors did a -- performed a statistical
 6 correction to address errors that may result from
 7 multiple endpoints or hypotheses like this?
 8 A Did I confirm? I did not confirm.
 9 Q Okay. And we have multiple endpoints at
 10 issue, and you don't do a statistical adjustment.
 11 Do you agree that increases a risk of
 12 type 1 error, a false-positive?
 13 A So I did not pose myself as an
 14 epidemiologist, nor a biostatistician. So
 15 therefore, like I said in my report, I stated
 16 myself as a pharmacologist who utilizes these
 17 things. So -- so therefore, you have to
 18 understand it's the scope of my abilities.
 19 Q Okay.
 20 A And I'm going to defer to the
 21 epidemiologists who's in this case.
 22 Q Did the Vlenterie authors -- did you
 23 give any less weight in your assessment of the
 24 Vlenterie study because it relied on screening
 25 tools instead of not actual diagnoses?

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1 A I stated the one that I thought was the
 2 highest weight, and I just -- and I think I stated
 3 the ones that are important for me were the
 4 drug -- where you could get drug levels, which is
 5 what a pharmacologist knows.
 6 Q Let me ask this: Would you -- did you
 7 give greater weight to Gustavson because it looked
 8 at ADHD clinical diagnoses than Vlenterie which
 9 did not look at ADHD clinical diagnoses?
 10 A I think the clinical diagnosis always
 11 gives me a little better --
 12 Q Did you say "better"?
 13 A You know, more weight.
 14 Q Okay.
 15 A Can I get rid of this?
 16 Q You can put this away.
 17 MS. KAPKE: We're on 31?
 18 MR. PADGETT: Yeah, I believe so.
 19 (Exhibit No. 31 was marked for
 20 identification.)
 21 BY MR. PADGETT:
 22 Q Dr. Louie, I'm handing you what's been
 23 marked as Exhibit 31, and it's a study called
 24 "Acetaminophen use in pregnancy: Examining the
 25 prevalence, timing and indication of use in a

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1 prospective birth cohort." It's a Bandoli 2019
 2 study.
 3 And while you're looking at that, I did
 4 not see this on your list of materials reviewed in
 5 your report. Have you read this?
 6 A (Peruses document.)
 7 This is not familiar.
 8 Q Okay. And then I assume that you did
 9 not take the findings in this study into account
 10 when coming to your opinion that there's an
 11 increased risk of ASD or ADHD in offspring of
 12 mothers who used acetaminophen 28 days or more
 13 during pregnancy; is that right?
 14 A (Peruses document.)
 15 Q My question is, did you take the
 16 findings of the study into account in coming to
 17 your opinion on the 28 days?
 18 Would you like to take a moment to
 19 review it?
 20 A Yeah, I -- this is the first time I've
 21 seen it.
 22 Q Take -- take a couple minutes, a few
 23 minutes.
 24 MR. PADGETT: We'll go off the record.
 25 THE VIDEOGRAPHER: Is this off the

<p style="text-align: right;">Page 154</p> <p>1 record? One moment.</p> <p>2 MR. ADAMS: Let's do this -- yeah, off</p> <p>3 the record, that's fine.</p> <p>4 THE VIDEOGRAPHER: Off the record at</p> <p>5 12:47.</p> <p>6 (Witness peruses document.)</p> <p>7 THE VIDEOGRAPHER: We are going back on</p> <p>8 the video record at 12:54 p.m.</p> <p>9 BY MR. PADGETT:</p> <p>10 Q Could you go to page 243 of Bandoli</p> <p>11 2019, right-hand column.</p> <p>12 A 240?</p> <p>13 Q 43. And do you see below Table 3 the</p> <p>14 sentence starting with "Any acetaminophen"? Do</p> <p>15 you see that?</p> <p>16 A Below the table. Can I read the</p> <p>17 entire --</p> <p>18 Q Paragraph? Go ahead, yes.</p> <p>19 A (Peruses document.)</p> <p>20 Q Are you done?</p> <p>21 A No. (Peruses document.) Okay.</p> <p>22 Q Okay. Do you see the sentence starting</p> <p>23 with "Any acetaminophen use," it states -- the</p> <p>24 authors state, quote: Any acetaminophen use and</p> <p>25 longer durations of use were both higher among</p>	<p style="text-align: right;">Page 156</p> <p>1 over lunch to find the data supporting that.</p> <p>2 My question is, were you -- are you</p> <p>3 aware of depression, anxiety, tobacco use, or use</p> <p>4 of antidepressants as being associated with</p> <p>5 increased risk of ASD or ADHD?</p> <p>6 A That's what it says in this sentence,</p> <p>7 but I wanted to see the data because you</p> <p>8 wouldn't -- you just -- give me -- let me finish.</p> <p>9 Let me finish.</p> <p>10 Q Go ahead. Go ahead.</p> <p>11 A Because you just want to read off of</p> <p>12 this, but I want to see the data, because</p> <p>13 sometimes a person who writes something, they may</p> <p>14 not show you the data, and what are they trying to</p> <p>15 hide? As an editor of a journal, I would say</p> <p>16 where does that -- where is that located?</p> <p>17 Q I understand, but we're missing each</p> <p>18 other.</p> <p>19 My question is not specifically related</p> <p>20 to this sentence. My question is, are you aware</p> <p>21 of tobacco use, anxiety, depression or</p> <p>22 antidepressant use being associated with ASD or</p> <p>23 ADHD in the scientific literature?</p> <p>24 MR. ADAMS: Object to form.</p> <p>25 THE WITNESS: I've seen the data. I'm</p>
<p style="text-align: right;">Page 155</p> <p>1 those with tobacco use in pregnancy, self-reported</p> <p>2 depression or anxiety and antidepressant use,</p> <p>3 period.</p> <p>4 Do you see that? Did I read that</p> <p>5 correctly?</p> <p>6 A You read that correctly, but I need to</p> <p>7 see the data associated with that. Was that --</p> <p>8 Q You've been able to review the report.</p> <p>9 My question is, are you aware of whether</p> <p>10 tobacco use, depression, anxiety or antidepressant</p> <p>11 use has been associated with ADHD or ASD?</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 THE WITNESS: So it -- I'm still back,</p> <p>14 where is the data?</p> <p>15 BY MR. PADGETT:</p> <p>16 Q My question is, are you aware of whether</p> <p>17 tobacco use, depression, anxiety or use of</p> <p>18 antidepressants has been associated with ADHD or</p> <p>19 ASD?</p> <p>20 MR. ADAMS: Object to form.</p> <p>21 THE WITNESS: Like I said to you, before</p> <p>22 you do that, I asked for a -- where's the data in</p> <p>23 association with that sentence?</p> <p>24 BY MR. PADGETT:</p> <p>25 Q As your counsel said, you can look at it</p>	<p style="text-align: right;">Page 157</p> <p>1 not an expert, so I'm not very -- I'm not</p> <p>2 comfortable in opining on that.</p> <p>3 BY MR. PADGETT:</p> <p>4 Q You've seen the data. So can you please</p> <p>5 answer my question: Are you aware of whether</p> <p>6 those risk factors have been associated with ASD</p> <p>7 or ADHD?</p> <p>8 MR. ADAMS: Object to form.</p> <p>9 BY MR. PADGETT:</p> <p>10 Q Yes, no, or I don't know.</p> <p>11 A I do -- yes.</p> <p>12 Q They have been associated.</p> <p>13 A They have been associated, but I don't</p> <p>14 know to the level. So -- I mean -- so you say I</p> <p>15 could read it, right, afterwards? So --</p> <p>16 MR. ADAMS: Don't worry about it. He</p> <p>17 asked you the question, and you've answered the</p> <p>18 question.</p> <p>19 MR. PADGETT: Take our lunch break?</p> <p>20 THE VIDEOGRAPHER: One moment. We're</p> <p>21 going off the record at 12:59 p.m.</p> <p>22 (Lunch recess.)</p> <p>23 THE VIDEOGRAPHER: We are going back on</p> <p>24 the video record at 1:59 p.m.</p> <p>25 BY MR. PADGETT:</p>

<p style="text-align: right;">Page 158</p> <p>1 Q Okay, Dr. Louie, back from lunch.</p> <p>2 If I could follow up on a couple of</p> <p>3 questions from something you said early today.</p> <p>4 You noted, and correct me if I'm wrong -- you say,</p> <p>5 I believe, that you give -- in terms of dosage,</p> <p>6 you gave a lot of weight to studies that showed</p> <p>7 epidemiology studies that showed concentration.</p> <p>8 Is that correct?</p> <p>9 A That is one of my assignments is to</p> <p>10 determine dosage and exposure. So anything that</p> <p>11 has both concentration and duration, I -- I weigh</p> <p>12 them higher.</p> <p>13 Q Okay. Which studies did you review and</p> <p>14 weigh higher in your analysis that involved</p> <p>15 concentration?</p> <p>16 A I think they both are in my report. I</p> <p>17 think G.</p> <p>18 Q G2018?</p> <p>19 A Yes, I think -- I forget the date. G --</p> <p>20 I think I have it here.</p> <p>21 I have the Baker. I think it's 2020.</p> <p>22 And then I have G -- oh, no, it's all messed up.</p> <p>23 I think it's -- there's -- it looks like 2020.</p> <p>24 Q G2020?</p> <p>25 A Yeah, I think so. Let me see if there's</p>	<p style="text-align: right;">Page 160</p> <p>1 maternal plasma in G2020?</p> <p>2 A I believe so.</p> <p>3 Q Okay. And so those -- G2020 and Baker</p> <p>4 2020 are studies that you relied on for</p> <p>5 concentration and gave great weight.</p> <p>6 A Well, there's -- sorry, there's one more</p> <p>7 paper.</p> <p>8 Q Okay.</p> <p>9 A Anand -- I don't even remember the year.</p> <p>10 A-N-A-N-D.</p> <p>11 Q Anand 2021?</p> <p>12 A (Peruses document.)</p> <p>13 Q It was Anand 2021.</p> <p>14 A Okay, I'll -- I'll believe that.</p> <p>15 Q And what -- how was concentration</p> <p>16 examined there?</p> <p>17 A Same thing, cord blood, cord plasma.</p> <p>18 Q Okay. Which of these -- did you give</p> <p>19 any of these three greater weight than the others?</p> <p>20 A When there's three studies, you give</p> <p>21 them all equal because you can review them all.</p> <p>22 Q Did you give meconium concentrations the</p> <p>23 same weight as cord blood or plasma</p> <p>24 concentrations?</p> <p>25 MR. ADAMS: Object to form.</p>
<p style="text-align: right;">Page 159</p> <p>1 another one.</p> <p>2 2020, it looks like. The G2020.</p> <p>3 Q G2020. Okay. And so Baker and G2020.</p> <p>4 Any others that you were relying on for</p> <p>5 concentration that you gave a lot of weight?</p> <p>6 A Those are -- those are the primary ones.</p> <p>7 Q And when you say they showed</p> <p>8 concentration, are you referencing Baker 2020</p> <p>9 because it involved meconium?</p> <p>10 A I believe that's -- that's what they</p> <p>11 use. It's by matrix.</p> <p>12 Q And G2020, how is concentration</p> <p>13 determined there?</p> <p>14 A Do you mind if I refer to my --</p> <p>15 Q Yes, please, go ahead.</p> <p>16 A It looks like they looked at cord blood.</p> <p>17 Q Cord blood?</p> <p>18 A Yes, umbilical cord blood.</p> <p>19 Q Was there a G2018 that you recall</p> <p>20 reviewing?</p> <p>21 A I -- I didn't bring that with me.</p> <p>22 Q Okay. It was cord plasma in G2020; is</p> <p>23 that right?</p> <p>24 A Yeah. Plasma is part of blood.</p> <p>25 Q And do you know whether they looked at</p>	<p style="text-align: right;">Page 161</p> <p>1 THE WITNESS: Why would I?</p> <p>2 BY MR. PADGETT:</p> <p>3 Q Would you agree that cord blood or</p> <p>4 plasma would only reflect acetaminophen exposure</p> <p>5 right around the time of delivery?</p> <p>6 A I've seen those discussion, but it may</p> <p>7 be not correct because we are assuming that the --</p> <p>8 the fetus's blood comes back to the mom as quick</p> <p>9 as the mom comes to the baby. And that's probably</p> <p>10 not true anymore.</p> <p>11 Q What do you mean by not anymore?</p> <p>12 A Well, the assumption was early onset</p> <p>13 that mother blood goes to fetus is equivalent to</p> <p>14 the -- from the fetus blood back to the mom was</p> <p>15 equal. There's now papers that suggest there is a</p> <p>16 difference between the two.</p> <p>17 Q And you're suggesting that this shows</p> <p>18 that cord blood would reflect doses of -- or</p> <p>19 concentrations of acetaminophen longer than a day</p> <p>20 or two?</p> <p>21 A I couldn't give you the time, but</p> <p>22 it's -- it could potentially be longer than we --</p> <p>23 we say, you know, greater than three hours.</p> <p>24 Q What do you mean, We say no longer than</p> <p>25 three hours?</p>

<p style="text-align: right;">Page 162</p> <p>1 A Well, the half-life -- people are</p> <p>2 referring to the half-life of acetaminophen about</p> <p>3 three hours. And that may not be true in the</p> <p>4 fetus.</p> <p>5 Q Do you have studies to indicate -- what</p> <p>6 studies indicate that the half-life of</p> <p>7 acetaminophen in a fetus is longer than three</p> <p>8 hours?</p> <p>9 A So as I stated to you, in order -- the</p> <p>10 baby doesn't have a way to urinate it out because</p> <p>11 it's still in mom, right?</p> <p>12 Q Mm-hmm.</p> <p>13 A So therefore, the blood has to be taken</p> <p>14 out of mom by mom, and then it's urinated out. So</p> <p>15 this is where the -- the half-life may be longer</p> <p>16 than we expected.</p> <p>17 Q The cord blood is shared by the mom and</p> <p>18 the fetus, right?</p> <p>19 A Well, the cord blood is mom's blood</p> <p>20 going to the baby. The baby has to come back out.</p> <p>21 That's how you expel -- I shouldn't say the baby.</p> <p>22 The fetus and the embryo comes back out.</p> <p>23 Q As you sit here today, can you name a</p> <p>24 study that shows that in the fetus the half-life</p> <p>25 for acetaminophen would be longer than three</p>	<p style="text-align: right;">Page 164</p> <p>1 pregnancy, and that was assessed -- a cumulative</p> <p>2 dose was assessed for the risk of that cumulative</p> <p>3 dose for ADHD, should your review have included</p> <p>4 that study if that was out there? Would you have</p> <p>5 been interested in that?</p> <p>6 MR. ADAMS: Object to form.</p> <p>7 THE WITNESS: So that's a different type</p> <p>8 of study, and if I remember correctly -- I need to</p> <p>9 look at this. When I did my search, I looked at a</p> <p>10 wide search, acetaminophen, pregnancy and autism.</p> <p>11 That's what -- and then switched the term to ADHD</p> <p>12 so to give a wide -- cast a wide net. I don't</p> <p>13 remember or recall seeing a paper.</p> <p>14 BY MR. PADGETT:</p> <p>15 Q Based on the description I just gave</p> <p>16 you, would you have liked to have seen that paper</p> <p>17 with that design evaluating cumulative dosage and</p> <p>18 risk of ADHD?</p> <p>19 A I -- I would review it.</p> <p>20 Q Would it be relevant to your opinions</p> <p>21 about dose, 28 days, and increased risk in this</p> <p>22 case?</p> <p>23 MR. ADAMS: Object to form.</p> <p>24 THE WITNESS: I couldn't tell without</p> <p>25 looking at the paper.</p>
<p style="text-align: right;">Page 163</p> <p>1 hours?</p> <p>2 A There are people who did placental</p> <p>3 half-life. So we don't do baby. So therefore in</p> <p>4 those papers, they show that it comes in X -- only</p> <p>5 0.5X come out during that time. So therefore that</p> <p>6 gives you the -- the information that it's</p> <p>7 probably half -- probably two times longer.</p> <p>8 Q Do you have -- is there a study?</p> <p>9 A There is, but I don't have it with me.</p> <p>10 Q Okay.</p> <p>11 A There is a study. There's actually more</p> <p>12 than one.</p> <p>13 Q If there was a study that used actual</p> <p>14 dosage from records for acetaminophen, and the</p> <p>15 study -- the authors of the study used those</p> <p>16 dosage records to calculate a cumulative dose for</p> <p>17 acetaminophen -- are you with me so far?</p> <p>18 A I'm not. I'm not. So when you say</p> <p>19 "records," what are you referring to?</p> <p>20 Q Medical records.</p> <p>21 A Oh, okay.</p> <p>22 Q If there was a study that used actual</p> <p>23 dosage from medical records or insurance records</p> <p>24 that showed -- that were used to calculate a</p> <p>25 cumulative dose of acetaminophen during a</p>	<p style="text-align: right;">Page 165</p> <p>1 (Exhibit No. 32 was marked for</p> <p>2 identification.)</p> <p>3 BY MR. PADGETT:</p> <p>4 Q Okay. You have before you Exhibit No.</p> <p>5 32, Dr. Louie. Do you recognize that study</p> <p>6 article?</p> <p>7 A This looks like a recent article by</p> <p>8 Olstad et al.</p> <p>9 Q And you talked about this in your reply.</p> <p>10 You called it a reply expert report, right?</p> <p>11 A I actually don't know --</p> <p>12 Q Rebuttal report, reply --</p> <p>13 A Yeah, yeah.</p> <p>14 Q We'll call it reply report. That's what</p> <p>15 it said.</p> <p>16 In your initial -- your amended expert</p> <p>17 report that is an exhibit here, you state that:</p> <p>18 "It is possible that fewer than 28 days of</p> <p>19 prenatal exposure to acetaminophen can increase</p> <p>20 offspring risk to develop ASD and ADHD." And you</p> <p>21 rely on the Gervin 2017 study.</p> <p>22 Do you recall that?</p> <p>23 A I did.</p> <p>24 Q Okay. And it's findings on DNA</p> <p>25 methylation, right?</p>

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1 A Yes.

2 Q Okay. So I want to ask you a couple --

3 a few questions about -- can you give me the title

4 of Exhibit 31, Olstad 2023. Can you read that

5 out, please.

6 A "No impact of prenatal paracetamol and

7 folic acid exposure on cord blood DNA methylation

8 in children with attention-deficit/hyper- --

9 hyperactivity disorder."

10 Q And do you have any understanding as to

11 whether the same research group that did the

12 Gervin 2017 study did this study in Olstad 2023

13 that's Exhibit 31?

14 A Say that again. I --

15 Q Do you have an understanding as to

16 whether the research team, the authors of Gervin

17 2017 is the same group that did Olstad 2023?

18 A I do, because Gervin is a coauthor.

19 Q Right. Same -- same group of coauthors,

20 same research team.

21 MR. ADAMS: Object to form.

22 THE WITNESS: I think similar. I don't

23 think it's exact.

24 BY MR. PADGETT:

25 Q Okay. If you could turn to page 2 of

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1 Olstad 2023, they go through and describe what

2 they're proposing to do there. I'm looking at the

3 left column, last paragraph.

4 And they talk about Gervin 2017 there,

5 right? Their previous -- they call it "our

6 previous study."

7 Do you see that?

8 A I see that.

9 Q Okay. And then they state, quote, in

10 the middle of that paragraph: To strengthen these

11 findings, we wanted to replicate and expand on a

12 previous study, both by increasing the number of

13 samples and CpGs, and by exploring whether folic

14 acid may impact a potential effect of paracetamol

15 on DNA methylation.

16 Did I read that correctly?

17 A Yes.

18 Q Paracetamol is acetaminophen, right?

19 A The Europeans refer to it as that.

20 Q Okay. So yes, right?

21 A Yes. Sorry.

22 Q And if you go to page 5, please.

23 A I didn't catch that.

24 Q Page 5.

25 And it's the last paragraph of this

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1 study before the data availability statement. Can

2 you read that sentence starting with "In

3 conclusion," please.

4 A "In conclusion, this study did not

5 replicate previous findings in the MoBa and other

6 studies investigating the influence of paracetamol

7 on DNA methylation, and did not identify any

8 interaction effect of paracetamol and folic acid

9 on DNA methylation in children with ADHD."

10 Did you want me to read it further?

11 Q No.

12 If you could also turn to page 5, the

13 left column, just a little bit farther down and

14 directly to the left there.

15 Do you see the first paragraph under

16 "Discussion"?

17 A Yes.

18 Q And -- if you want to look at that

19 paragraph, that's fine, but it -- it states

20 there -- the authors state that their findings

21 were surprising as it was based on a large number

22 of samples from the same cohort as Gervin 2017,

23 right?

24 A Yes.

25 Q And then they note, quote: However, our

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1 studies are performed five years apart and methods

2 have evolved, including the introduction of

3 Illumina Infinium EPIC platform and novel analysis

4 methods, such as normalization and cell type

5 deconvolution procedures.

6 Did I read that right?

7 A You did.

8 Q Okay. And then if you could turn to

9 paragraph 44 of your reply report.

10 A I'm sorry --

11 Q If you could turn to page -- to page 21

12 of your reply report, paragraph 44. Page 22 --

13 A Oh, okay.

14 Q -- paragraph 44.

15 A 22?

16 Q Paragraph 44. That would probably be

17 the easiest way.

18 A Okay. And 22 is not -- are you sure?

19 44 is --

20 Q Paragraph 44?

21 A Is 21.

22 Q Okay. Paragraph 44, you -- you state

23 that the Olstad study employed a different

24 technology for detecting DNA methylation

25 differences than the one used in Gervin, and that

<p style="text-align: right;">Page 170</p> <p>1 Olstad analyzed approximately 850,000 CpG sites</p> <p>2 across -- across the genome, and Gervin analyzed</p> <p>3 approximately 450,000 CpG sites at CpG islands and</p> <p>4 promoters.</p> <p>5 A Mm-hmm.</p> <p>6 Q And you point -- this is a</p> <p>7 methodological difference that may explain the</p> <p>8 differences in the outcomes.</p> <p>9 Are you saying that -- that there's</p> <p>10 something wrong with the methodology used in</p> <p>11 Olstad 2023 here, some type of scientific</p> <p>12 reliability issue?</p> <p>13 A No, no, no. It's actually very simple.</p> <p>14 The 850 tells you that this is a more sensitive</p> <p>15 instrument. It's able to look at a wider</p> <p>16 spectrum. This instrument is actually -- will</p> <p>17 give you more noise because if you're more</p> <p>18 sensitive, you're going to have more noise.</p> <p>19 That's the key element in the analysis.</p> <p>20 And that's one of the things that I</p> <p>21 thought when I looked at Olstad, wonderful study,</p> <p>22 they need to show me where the cutoff was, and I</p> <p>23 didn't see that in that paper. So that was a</p> <p>24 disappointment, but for what it's worth, they</p> <p>25 showed a different analyses.</p>	<p style="text-align: right;">Page 172</p> <p>1 A Mm-hmm.</p> <p>2 Q Is that your primary -- a primary</p> <p>3 concern of yours with this study as to why it may</p> <p>4 have failed to replicate Gervin 2017?</p> <p>5 I know you're --</p> <p>6 A So what are you telling me on Figure 1?</p> <p>7 Q Is that -- what you said is that they</p> <p>8 failed to adjust for folic acid intake. Is that a</p> <p>9 primary concern you have about the methodology of</p> <p>10 Olstad 2023?</p> <p>11 A Yeah, it -- here it says "folic acid</p> <p>12 exposure," right?</p> <p>13 Q If you look at Figure 1, the</p> <p>14 description B says: "Adjusted model adjusting for</p> <p>15 folic acid intake during pregnancy and CD8 T-cell</p> <p>16 proportion."</p> <p>17 Do you see that?</p> <p>18 A B is folic acid intake, yes.</p> <p>19 Q Doesn't that indicate that they adjusted</p> <p>20 for folic acid intake in this study?</p> <p>21 A But I did not see them actually test it</p> <p>22 for folic acid. Am I wrong?</p> <p>23 Q Go a little below that.</p> <p>24 A Uh-huh.</p> <p>25 Q And just below Figure 1 on the left</p>
<p style="text-align: right;">Page 171</p> <p>1 Q With more sample sizes, correct?</p> <p>2 A Correct, but there's one point that you</p> <p>3 need -- probably need to add to this is that they</p> <p>4 added folic acid. I don't -- I don't know if you</p> <p>5 saw what folic acid does, but folic acid is key in</p> <p>6 changing methylation. It's well known.</p> <p>7 So I think that was not the best idea,</p> <p>8 that you add folic acid as -- as a factor, because</p> <p>9 there's a lot of data that shows that folic acid</p> <p>10 makes the precursors that methylates DNA.</p> <p>11 Q Well, they state, I'm looking at the</p> <p>12 abstract: "We did not identify any impact of</p> <p>13 paracetamol or any interaction effect of</p> <p>14 paracetamol and folic acid on cord blood DNA</p> <p>15 methylation in children with ADHD."</p> <p>16 Did they test acetaminophen separately</p> <p>17 to look at DNA methylation, and additionally with</p> <p>18 folic acid, right?</p> <p>19 A Yeah.</p> <p>20 MR. ADAMS: Object to form.</p> <p>21 THE WITNESS: One of the key elements of</p> <p>22 this is they didn't adjust for folic acid intake.</p> <p>23 Women who are pregnant have folic acid intake.</p> <p>24 BY MR. PADGETT:</p> <p>25 Q Could you turn to Figure 1.</p>	<p style="text-align: right;">Page 173</p> <p>1 column, starting with the word -- the sentence</p> <p>2 that says "We." And it says, quote: We then</p> <p>3 assessed whether folic acid could influence the</p> <p>4 association between paracetamol exposure in DNA</p> <p>5 methylation by running an adjusted model adjusting</p> <p>6 for folic acid intake during pregnancy. Correct?</p> <p>7 A So they adjusted with folic acid intake,</p> <p>8 but they didn't adjust it for the folic acid in</p> <p>9 the blood.</p> <p>10 Q And earlier you said your criticism was</p> <p>11 about not adjusting for folic acid intake, right?</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 THE WITNESS: But if you don't take</p> <p>14 it -- if you take it, you need to also look at it</p> <p>15 in the blood. They're drawing it, they could do</p> <p>16 it in the blood. It would not be hard.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q Could an explanation for the failure to</p> <p>19 replicate Gervin 2017 and Olstad 2019 also be that</p> <p>20 they had more data and more evolved methodology?</p> <p>21 A Yes. So when you say "improved</p> <p>22 methodology," you also increase noise. This is</p> <p>23 where something that we always worry about when we</p> <p>24 start to use improved technologies.</p> <p>25 So I didn't see that there was a cutoff</p>

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1 as to the sensitivity of these assays or did they
 2 take all comers.
 3 Q Could you turn to your report -- is it
 4 Exhibit 1? Or, sorry, Exhibit 21, your big
 5 report.
 6 A What was it, the -- the big report.
 7 Q Yeah.
 8 A Mm-hmm. And what page?
 9 Q We're going to talk about pages 39 and
 10 40.
 11 A Okay, I'm there.
 12 Q Okay. And there, 39 and 40, you discuss
 13 the process for how acetaminophen is metabolized,
 14 right?
 15 A Yes.
 16 Q Okay. I have some questions about that.
 17 Do you agree that when acetaminophen is taken
 18 orally, it must first pass through the liver?
 19 A It doesn't first pass the liver. It
 20 first passes the gut first, yeah.
 21 Q Small intestine first, I guess, but then
 22 it has to pass through the liver, correct?
 23 A Before it gets to circulation, yes.
 24 Q Okay. You agree that a portion of
 25 acetaminophen is metabolized during the pass

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1 through the liver?
 2 A The acetaminophen goes to the liver and
 3 gets metabolized. Yes.
 4 Q And would you agree the amount of
 5 acetaminophen that reaches other organs, including
 6 the placenta and reproductive organs, is lower
 7 than the amount actually ingested because of that
 8 metabolism in the liver?
 9 A So the blood levels when we take it, we
 10 don't know -- actually know what's in the -- in
 11 the -- unless we take a needle and put it into the
 12 intestines, we don't know what the level is that's
 13 absorbed. So -- but when we draw from the blood,
 14 it's already past the liver.
 15 Q If it's metabolizing acetaminophen -- in
 16 the liver, acetaminophen, some of it is getting
 17 converted and won't be as high when it moves on
 18 from the liver. Do you agree with that?
 19 A That's the concept, yeah, but I want to
 20 make sure you understood that the blood -- the
 21 level in the blood is already past the liver.
 22 Q And by the time it gets to the blood,
 23 it's going to be lower than it was when it was
 24 taken as an oral dose. Do you agree with that?
 25 MR. ADAMS: Object to form.

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1 THE WITNESS: It depends on the time.
 2 BY MR. PADGETT:
 3 Q What do you mean by "it depends on the
 4 time"?
 5 A So oral absorption takes time to absorb.
 6 So you're talking about the Cmax, right? This is
 7 what you're referring to. Cmax goes up in one
 8 hour, so therefore approximately one hour. It
 9 does come down right after that. So -- I'm trying
 10 to understand what your question --
 11 Q I believe you also -- you agree that the
 12 half-life of acetaminophen is generally considered
 13 to be one to three hours. I think on page 58 of
 14 your report at the bottom, it notes 84 minutes,
 15 right?
 16 A Yeah. In general, in a healthy -- in a
 17 healthy individual, that's approximately it.
 18 Q Do you agree that the concentration of
 19 acetaminophen generally becomes undetectable
 20 within 10 to 12 hours unless another dose is
 21 taken?
 22 A It depends on the assay you used today.
 23 If you use a mass spec, you will see it past 24
 24 hours.
 25 Q You indicated that you had reviewed

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1 Dr. Pearson's report, right?
 2 A I believe so.
 3 Q Okay. And do you recall him saying that
 4 after, quote, After eight hours, only small
 5 amounts of the drug are detectable in the plasma,
 6 end quote?
 7 A I don't recall. But if you have it,
 8 I'll --
 9 Q Do you have any reason to disagree with
 10 that statement?
 11 A If you use HPLC, it's a little -- it
 12 will go away faster. If you use LC-MS, you have a
 13 magnitude of a thousandfold more sensitivity.
 14 Q Would you agree that acetaminophen is
 15 metabolized in the liver -- and if you want to
 16 look at pages 39 and 34 of your report.
 17 A Mm-hmm.
 18 Q You agree that acetaminophen is
 19 metabolized in the liver through three main
 20 pathways of glucuronidation, sulfation and
 21 oxidation?
 22 A Glucuronidation, sulfation, and
 23 glutathione -- well, I -- you -- yeah, that's
 24 actually not true. But cytochrome P450 makes the
 25 metabolite, and then it's glucuronidated -- no,

<p style="text-align: right;">Page 178</p> <p>1 sorry, it's glutathione.</p> <p>2 I will -- sorry, I'm going to mess up</p> <p>3 because it's going to be two different ways.</p> <p>4 Q So when you say oxidation, that is the</p> <p>5 GSH binding with any NAPQI that would be</p> <p>6 present --</p> <p>7 A Yes.</p> <p>8 Q -- and turning it into a harmless</p> <p>9 metabolite.</p> <p>10 MR. ADAMS: Object to form.</p> <p>11 THE WITNESS: So you're saying NAPQI --</p> <p>12 I'm not used to hearing that Napkey (phonetic).</p> <p>13 You're saying that cytochrome P450</p> <p>14 converts acetaminophen to NAPQI, and it binds very</p> <p>15 quickly to glutathione or anything with a</p> <p>16 cysteine. So any -- any protein nearby with a</p> <p>17 cysteine, NAPQI Y can actually interact with.</p> <p>18 BY MR. PADGETT:</p> <p>19 Q And you say CYP450. Is the primary --</p> <p>20 the enzyme that acetaminophen would combine with</p> <p>21 to create NAPQI, is that CYP2E1?</p> <p>22 A So you're saying acetaminophen</p> <p>23 biotransformed to NAPQI Y, you're saying is only</p> <p>24 one enzyme. The answer is it's not just one</p> <p>25 enzyme. Cytochrome P450 IIE1 may be the</p>	<p style="text-align: right;">Page 180</p> <p>1 from Dr. McGill in his expert report.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q Do you agree that a small fraction of</p> <p>4 acetaminophen is excreted unchanged in the urine?</p> <p>5 A And that small fraction is about 2 --</p> <p>6 3 percent. Yes.</p> <p>7 Q Okay. Once GSA binds to NAPQI in the</p> <p>8 liver, it converts it into a harmless metabolite</p> <p>9 that's excreted in the urine, correct?</p> <p>10 A So you're saying the formation of NAPQI</p> <p>11 binds with the GSH, and that in itself is</p> <p>12 neutralized. And it can also bind on to</p> <p>13 anything -- any protein with sulfhydryl group --</p> <p>14 that means the SH group -- and that can cause</p> <p>15 toxicity.</p> <p>16 Q Do you address this SH group toxicity in</p> <p>17 your report?</p> <p>18 A I did. I did tell you in the report</p> <p>19 that NAPQI can form protein adducts, and maybe</p> <p>20 that's -- and not 100 percent of all NAPQI is</p> <p>21 bounded by GSH.</p> <p>22 Q Okay. Do you agree that potential</p> <p>23 damage from NAPQI is dependent on whether there's</p> <p>24 a sufficient amount of GSH compared to the NAPQI?</p> <p>25 MR. ADAMS: Object to form.</p>
<p style="text-align: right;">Page 179</p> <p>1 predominant. And cytochrome P450 IIIA4 --</p> <p>2 THE REPORTER: Doctor, could I get you</p> <p>3 to slow down a little bit.</p> <p>4 THE WITNESS: Sorry.</p> <p>5 THE REPORTER: May be the predominant?</p> <p>6 THE WITNESS: Cytochrome P450 IIIA4 and</p> <p>7 5, and cytochrome P450 IA1 can also do that.</p> <p>8 BY MR. PADGETT:</p> <p>9 Q Do you agree that approximately 85 to 95</p> <p>10 percent of acetaminophen is conjugated through</p> <p>11 glucuronide or sulfate and excreted in the urine?</p> <p>12 A Can you give me the number again? I'm</p> <p>13 sorry.</p> <p>14 Q Eighty-five to 95 percent.</p> <p>15 A That's -- there's a range, yeah.</p> <p>16 That -- that range is pretty close.</p> <p>17 Q Okay. And when you say "pretty close,"</p> <p>18 do you believe it's lower than that, higher?</p> <p>19 MR. ADAMS: Object to form.</p> <p>20 THE WITNESS: So when you ask the</p> <p>21 question, in essence, you used the highest level</p> <p>22 because there's a range for glucuronidation and</p> <p>23 sulfation. So the cytochrome P450 can contribute</p> <p>24 to between 5 percent and 10 percent of total</p> <p>25 metabolism. I believe I got most of that data</p>	<p style="text-align: right;">Page 181</p> <p>1 THE WITNESS: Can you rephrase that?</p> <p>2 MR. PADGETT: Can you just read it back,</p> <p>3 please?</p> <p>4 THE REPORTER: "Do you agree that</p> <p>5 potential damage from NAPQI" --</p> <p>6 THE WITNESS: QI.</p> <p>7 THE REPORTER: -- "QI is dependent on</p> <p>8 whether there's a sufficient amount of GSH</p> <p>9 compared to the NAPQI?"</p> <p>10 MR. ADAMS: Object to form.</p> <p>11 THE WITNESS: So glutathione has to</p> <p>12 overwhelm the level of NAPQI to neutralize it.</p> <p>13 Even when it's overwhelming, the NAPQI can escape</p> <p>14 the GSH. That's pretty well known.</p> <p>15 BY MR. PADGETT:</p> <p>16 Q When you say "escape," what do you mean,</p> <p>17 by what process?</p> <p>18 A It can -- it can bind on to other</p> <p>19 proteins, so therefore forms the protein adduct.</p> <p>20 That's information well known that -- that even at</p> <p>21 conventional doses, you can form a lot of NAPQI</p> <p>22 adducts or acetaminophen adducts.</p> <p>23 Q Are you aware of any scientific studies</p> <p>24 that show that these other protein adducts result</p> <p>25 in a biological change in the brain that leads to</p>

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1 autism spectrum disorder?

2 A So you reframed the question. So first,

3 it occurs in papers that shows that children who

4 take acetaminophen at normal doses, about 3 to 5

5 percent of them will have extremely high level of

6 acetaminophen adducts. This is a clinical study

7 that was done in children.

8 You asked a second question, does that

9 relate to the brain? I do not know if there's

10 such a paper.

11 Q Okay.

12 A But when you start to look at the

13 formation of protein adducts in the blood, it

14 suggests that it can actually do this.

15 Q When you say, "It can actually do this,"

16 what do you mean by that?

17 A That the NAPQI can bind the proteins and

18 in large levels, even at normal concentrations.

19 Q Do you agree that the amount of NAPQI is

20 dependent on the amount of -- predominantly

21 dependent on the amount of CYP2E1?

22 MR. ADAMS: Object to form.

23 THE WITNESS: Yes.

24 BY MR. PADGETT:

25 Q And you state -- you state -- it's

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1 page -- it's paragraph 105 of your amended report,

2 page 40.

3 A Page 40?

4 Q Yes. Are you there?

5 A I'm there.

6 Q Let me back up and ask a quick question.

7 Are you aware of any human studies showing damage

8 from NAPQI in liver or anywhere from a therapeutic

9 dose level of acetaminophen?

10 A I just referred you to that children's

11 study that kids who got more than one dose of

12 acetaminophen, they started developing protein

13 adducts of acetaminophen, which indicates, even in

14 Dr. McGill's own -- own report, that that is a

15 sign of mitochondrial toxicity.

16 Q Which report -- which study are you

17 talking about?

18 A Dr. McGill, who was the expert witness,

19 says that the protein adducts of -- of

20 acetaminophen was an indicator of mitochondrial

21 toxicity.

22 Q And, are you aware -- again, are you

23 aware of a human study showing -- your position is

24 that -- your opinion is that a showing of

25 mitochondrial toxicity is equivalent to damage

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1 from NAPQI?

2 MR. ADAMS: Object to form.

3 THE WITNESS: I actually probably

4 have -- I actually refer to a paper that's in my

5 report, Jetton et al., and they use therapeutic

6 doses at half a gram to 2 grams to 4 grams, and

7 they were able to detect cellular hepatotoxicities

8 at normal doses -- or therapeutic doses.

9 BY MR. PADGETT:

10 Q And this study was focused on the liver,

11 correct?

12 A No, that was focused on the

13 transcriptomic data. They show that there's

14 oxidative stress, and it shows apoptosis of cells,

15 which is -- it means programmed cell death at

16 4 grams a day.

17 Q You mentioned sample size a couple of

18 times as an issue.

19 MR. PADGETT: Let's go ahead and make

20 that an exhibit.

21 (Exhibit No. 33 was marked for

22 identification.)

23 BY MR. PADGETT:

24 Q How many subjects were there in the

25 Jetton study?

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1 A There were seven, but this is what we

2 call a crossover study, which is -- for

3 pharmacologists, is considered the best study.

4 They looked over concentration over time.

5 Q I'm going to hand you what's been marked

6 as -- what are we on?

7 MS. KAPKE: 33.

8 BY MR. PADGETT:

9 Q I'm going to hand you what's been marked

10 as Exhibit 33. Is that the Jetton study that

11 you're referring to?

12 A (Peruses document.) This is.

13 Q And looking -- this involve -- this

14 involved a 2-gram dose, or is that two 1-gram

15 doses?

16 A Yeah, they -- it's -- it's actually 500

17 milligrams given four times a day.

18 Q And do you recall Dr. Powell

19 criticized -- took issue with whether this study

20 had a sufficient sample size? I think you talked

21 about that in your reply report.

22 A Yeah. Well, I want to thank Dr. Powell

23 for being incorrect, because he's not a

24 pharmacologist. In fact, this is the best study

25 that I could recommend to do dose escalating

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1 studies.

2 In my report I explain that each patient

3 is their own control. And in my study, this is

4 what a pharmacologist does in determining dose

5 effects.

6 And in this study, they -- they actually

7 detected in -- I believe page 327, they concluded

8 and says 24-hour ingestion of 4 grams of APAP in

9 metabolomic response, very similar to 2 grams, was

10 detected with high levels of hepatic toxic related

11 metabolites.

12 Q I'm looking at the last paragraph there

13 on that same page.

14 A Mm-hmm.

15 Q And the language that says: "Our study

16 having in itself sufficient -- insufficient

17 numbers of volunteers to evaluate this may provide

18 a model for exploring such interindividual

19 variability in drug responses."

20 Aren't the authors there indicating that

21 they had concerns about the number of having only

22 seven individuals in the study?

23 A Actually, offering a limitation, but if

24 you were to expand this, you would probably get --

25 because they got statistically significant in

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1 seven patients.

2 So this is -- as I stated, every

3 research paper we always highlight our

4 limitations. That's talking about potential

5 errors. It doesn't mean that they are really

6 errors.

7 Q If you could go -- sorry, I'm bouncing

8 around a bit, but if you go back to page 40 of

9 your report.

10 A Can I put this down? Page --

11 MR. ADAMS: Are we in the original or --

12 MR. PADGETT: The original. Yeah, the

13 amended, July 21, I think.

14 BY MR. PADGETT:

15 Q You indicate -- I'm looking at the

16 sentence, "However," you state that: "... at high

17 systemic acetaminophen concentrations (as a

18 consequence of ingesting higher sustained dosages

19 of acetaminophen), the body's endogenous levels of

20 GSH are reduced, and as a consequence, they may

21 become unable to accommodate the excess NAPQI

22 levels that are produced."

23 Did I read that right?

24 A Mmm, I don't think you read it right.

25 Q What did I --

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1 A It says "as a consequence of ingesting

2 high or sustained dosages." So it's -- they're

3 separated. It's not just high, it's also

4 sustained.

5 Q And when you state "sustained doses of

6 acetaminophen," are you referring to therapeutic

7 doses there?

8 A That is what I'm relating to you.

9 Q And by "high doses," are you referring

10 to higher than therapeutic doses?

11 A I am.

12 Q Okay. Were you -- I don't know if we

13 confirmed this. You agree that lower levels of

14 CYP2E1 generally would result in lower levels of

15 NAPQI conjugated by -- or produced by a

16 combination of -- strike that.

17 You agree that lower levels of CYP2E1 at

18 a particular site in the body would generally mean

19 that there would be lower levels of NAPQI produced

20 at that site.

21 A It depends.

22 And let me qualify for you what I mean.

23 One of the things that is missing in all

24 the analyses is that cytochrome P450 IIE1 is an

25 inducible enzyme. And what I mean by that, you

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1 use it once, the body will upregulate its enzyme.

2 In my report, I tell you it doesn't go

3 up just one time or two times, it goes up tenfold.

4 Q And that is based on the, I believe --

5 MR. ADAMS: He wasn't finished with his

6 answer --

7 MR. PADGETT: Oh, sorry.

8 MR. ADAMS: -- Counsel.

9 MR. PADGETT: I thought you were.

10 THE WITNESS: And so how high it

11 actually goes could be much higher.

12 I'm done.

13 BY MR. PADGETT:

14 Q Much higher than the tenfold you discuss

15 in your reply report?

16 A It potentially can. Because most of

17 these studies are only done for a specific amount

18 of time. So I don't know what the entire effect

19 over 28 days or 30 days would do.

20 Q And I believe I saw in your reply

21 report, you're relying primarily on the Posadas

22 study for that ten times inducement?

23 A No, the Posadas study was one. Kim

24 and -- Kim et al. showed it in animals. And in

25 fact, two doses they showed that there was a

<p style="text-align: right;">Page 190</p> <p>1 tenfold increase.</p> <p>2 Q Tenfold in the Kim study?</p> <p>3 A Yeah.</p> <p>4 Q Okay.</p> <p>5 A In the protein levels, if you look very</p> <p>6 carefully at -- at their -- and they also show</p> <p>7 enzymatic activity.</p> <p>8 Q Kim was focused on microphages -- lung</p> <p>9 microphages; is that right?</p> <p>10 A I think you got the wrong study.</p> <p>11 Q Okay. We'll get to Kim and Posadas here</p> <p>12 in a moment.</p> <p>13 Do the levels of GSH in CYP2E1 differ</p> <p>14 across different parts of the human body?</p> <p>15 A It should.</p> <p>16 Q And in your reply report, I think it's</p> <p>17 paragraph 13, you quote Dr. McGill's report where</p> <p>18 he states that the typical liver glutathione</p> <p>19 concentration is 5 to 10 millimole per liter.</p> <p>20 A I don't know where you went. Can you</p> <p>21 show --</p> <p>22 Q In paragraph 13 of your reply report.</p> <p>23 A Paragraph 13.</p> <p>24 Q My question is, based on scientific</p> <p>25 literature, do you agree that 5 to 10 millimoles</p>	<p style="text-align: right;">Page 192</p> <p>1 reviewed when making -- drafting your reply report</p> <p>2 dated June -- July 28, 2023?</p> <p>3 A Sorry about that. I want to make</p> <p>4 sure -- okay. It appears so.</p> <p>5 Q And I just want to confirm this. At</p> <p>6 paragraphs -- you state at paragraph 6 of your</p> <p>7 reply report, quote: This he indicates results in</p> <p>8 a diminished capacity for the brain to neutralize</p> <p>9 any NAPQI produced within it, period, end quote.</p> <p>10 Did I read that right?</p> <p>11 A I'm sorry. I think in my report --</p> <p>12 where are you -- where are you --</p> <p>13 Q Paragraph 6.</p> <p>14 A Paragraph -- okay.</p> <p>15 Q The last paragraph there.</p> <p>16 A Yes, I said that.</p> <p>17 Q Could you turn to paragraph 4 of</p> <p>18 Dr. McGill's report, please.</p> <p>19 In paragraph 4, wouldn't you agree that</p> <p>20 Dr. McGill, if anything, says the opposite by</p> <p>21 stating, quote: There is no scientific evidence</p> <p>22 of NAPQI formation in the human embryonic/fetal</p> <p>23 brain sufficient to cause injury following</p> <p>24 maternal ingestion of therapeutic doses of</p> <p>25 acetaminophen?</p>
<p style="text-align: right;">Page 191</p> <p>1 per liter is a typical concentration for GSH in</p> <p>2 the liver?</p> <p>3 A That's what Dr. McGill says. Yeah, I</p> <p>4 have no reason to -- to disagree with him.</p> <p>5 Q Okay. And then paragraph 6 of your</p> <p>6 reply report --</p> <p>7 A Paragraph --</p> <p>8 Q -- you state that Dr. McGill indicates</p> <p>9 that the brain glutathione levels is 1 to 2</p> <p>10 micromolar per milliliter, and that's a</p> <p>11 concentration five times lower than the typical</p> <p>12 hepatic GSH concentration.</p> <p>13 Do you see that?</p> <p>14 A I see that.</p> <p>15 Q And then you say: "This he indicates</p> <p>16 results in a diminished capacity for the brain to</p> <p>17 neutralize any NAPQI produced within it."</p> <p>18 Where do -- where did Dr. McGill make</p> <p>19 that statement in his report? Do you --</p> <p>20 A I would need to see Dr. McGill's report.</p> <p>21 (Exhibit No. 34 was marked for</p> <p>22 identification.)</p> <p>23 BY MR. PADGETT:</p> <p>24 Q I hand you what's been marked as</p> <p>25 Exhibit 34. Is that Dr. McGill's report that you</p>	<p style="text-align: right;">Page 193</p> <p>1 A He's making that as a conclusion, but</p> <p>2 his own data suggests -- because the liver has 5</p> <p>3 to 10 micromoles per mL, the brain has 1 to 2.</p> <p>4 I mean, I could do the regular math.</p> <p>5 That's a five- to tenfold differences between the</p> <p>6 brain and the liver. I mean, he could make a</p> <p>7 statement, but if you do the math on his</p> <p>8 statement, that's not true.</p> <p>9 Q And you're talking about GSH there?</p> <p>10 A I am.</p> <p>11 Q Okay. Do you agree that levels of</p> <p>12 CYP2E1 in the brain and liver differ?</p> <p>13 A That's what the data seem to show.</p> <p>14 Q Have you reviewed The Human Protein</p> <p>15 Atlas source that was referenced in Dr. McGill's</p> <p>16 report?</p> <p>17 A I did. I did look at it, and he shows</p> <p>18 an mRNA of I think 1000-fold less than that of --</p> <p>19 of that in the liver.</p> <p>20 Q In the brain --</p> <p>21 A Versus the liver, right.</p> <p>22 Q The CYP2E1 is 1000-fold less in The</p> <p>23 Human Protein Atlas than that seen in the liver.</p> <p>24 Correct?</p> <p>25 A The problem is that The Human Protein</p>

<p style="text-align: right;">Page 194</p> <p>1 Atlas, he's quoting RNA, which is not protein.</p> <p>2 Let me finish.</p> <p>3 And what's also important, even in his</p> <p>4 own -- I think in his own papers that he quotes, I</p> <p>5 think it's Warren et al., and they showed that the</p> <p>6 protein levels were between 1 to 5 percent of</p> <p>7 that. So therefore, 1 to 5 percent is not a</p> <p>8 thousandfold less.</p> <p>9 Q You're talking about Warner 1988?</p> <p>10 A Yeah.</p> <p>11 Q Does Warner 1988 reference CYP2E1</p> <p>12 specifically in any way?</p> <p>13 A Do you have the paper?</p> <p>14 Q I do.</p> <p>15 MR. PADGETT: Get Warner.</p> <p>16 (Exhibit No. 35 was marked for</p> <p>17 identification.)</p> <p>18 BY MR. PADGETT:</p> <p>19 Q I'm handing you what's been marked as</p> <p>20 Exhibit 35, which is the Warner 1988, correct?</p> <p>21 Exhibit 35, Warren -- Warner 1988?</p> <p>22 A Yeah. 1988, yes.</p> <p>23 Q Okay. And that -- that study is about</p> <p>24 CYP450 proteins broadly, right?</p> <p>25 MR. ADAMS: Object to form.</p>	<p style="text-align: right;">Page 196</p> <p>1 Q Dr. Louie, we printed out materials from</p> <p>2 the protein -- Human Protein Atlas, and</p> <p>3 recognizing it's a full website, does that look</p> <p>4 like material from The Human Protein Atlas?</p> <p>5 A Yes, and -- I don't think these are</p> <p>6 protein again. Let's see if it says protein.</p> <p>7 They use antisense in page 17 of 17. I</p> <p>8 could be wrong.</p> <p>9 Q If you could look six pages in.</p> <p>10 A Six.</p> <p>11 2 of 3, is that the one in the bottom?</p> <p>12 Q 1 of 5.</p> <p>13 A 1 of -- huh?</p> <p>14 Q Two, four -- sorry, 11. Eleven pages</p> <p>15 in.</p> <p>16 A One, two, three -- is it this? Make</p> <p>17 sure I got the right --</p> <p>18 Q No. It's the one that says "CYP2E1," 1</p> <p>19 of 5, 8/2/2023, 8:57 p.m.</p> <p>20 A Is that the correct one?</p> <p>21 Q Yes. And, Dr. Louie, that shows the</p> <p>22 cerebellum of The Human Protein Atlas in CYP2E1,</p> <p>23 and it shows protein expression.</p> <p>24 A Mm-hmm.</p> <p>25 Q And cells -- "Cells in granular layer,</p>
<p style="text-align: right;">Page 195</p> <p>1 THE WITNESS: Correct. But in a</p> <p>2 follow-up by the same authors, in Hansson et al.,</p> <p>3 1990, they specifically use cytochrome P450 IIE1.</p> <p>4 BY MR. PADGETT:</p> <p>5 Q In your reply report you talk about</p> <p>6 Warner 1988 --</p> <p>7 A And --</p> <p>8 Q -- and then you state that Dr. McGill</p> <p>9 falsely -- and this is paragraph 36 of your reply</p> <p>10 report -- falsely represents the levels of CYP2E1</p> <p>11 are much lower than what Warner et al.'s research</p> <p>12 actually finds, end quote.</p> <p>13 A So if you go back to my paragraph 17, 8,</p> <p>14 I refer to it as -- in fact, I don't know how you</p> <p>15 pronounce it -- to Hansson, and that was the first</p> <p>16 author. And you see that in the -- 8 refers to a</p> <p>17 cytochrome P450 IIE1. Very specific.</p> <p>18 That's in my report, page 8,</p> <p>19 paragraph 17, line -- one, two, three -- line 3.</p> <p>20 MR. PADGETT: 35?</p> <p>21 THE REPORTER: The next one?</p> <p>22 MR. PADGETT: Is 36?</p> <p>23 (Exhibit No. 36 was marked for</p> <p>24 identification.)</p> <p>25 BY MR. PADGETT:</p>	<p style="text-align: right;">Page 197</p> <p>1 molecular layer, Purkinje cells not detected."</p> <p>2 Do you see that?</p> <p>3 A I see that.</p> <p>4 Q Okay. And the -- the mRNA expression</p> <p>5 for CYP2E1 is 12.7. Correct, for the consensus?</p> <p>6 A Where are you seeing that?</p> <p>7 Q Just below Purkinje cells.</p> <p>8 A Purkinje consensus. I mean, how did</p> <p>9 you -- sorry.</p> <p>10 Q nTPM -- 12.7 nTPM. Do you see that?</p> <p>11 A That's the RNA?</p> <p>12 Q Yes.</p> <p>13 A It's not referenced as RNA. That's why</p> <p>14 I'm trying to figure out --</p> <p>15 Q And is it your understanding nTPM means</p> <p>16 normalized transcript per million?</p> <p>17 A Correct.</p> <p>18 Q Okay. And could you turn about five</p> <p>19 pages later.</p> <p>20 A Before you do that, I have to ask a</p> <p>21 question because I haven't looked through this --</p> <p>22 Q Okay.</p> <p>23 A -- completely.</p> <p>24 The next page after the page that you</p> <p>25 talked to me about, is that cerebellum that's</p>

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1 standing for cytochrome P450 IIE1?

2 Q Yes.

3 A Am I seeing this wrong? It's -- in the

4 blue, is that positive?

5 Q I'd have to look at it, Dr. Louie.

6 I'm --

7 A I'm just asking the question because

8 I -- I have not seen this document.

9 Q You said you reviewed the --

10 A Just because I review it -- did you see

11 this?

12 Q Okay. Yeah.

13 A It doesn't mean I go look through

14 everything. And so to be fair, got it. Fair

15 enough. Thank you.

16 Q Did you -- when you were reviewing this,

17 did you look to see what the liver levels for

18 CYP2E1 were?

19 A So I have issues looking at databases

20 because there may be a few samples. I like to see

21 published papers, and the published papers are

22 telling me otherwise.

23 And this is, although maybe the latest

24 and greatest, in old papers it tells me in 1990,

25 that it's expressed in the cytochrome P450 IIE1.

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1 Q Well --

2 MR. PADGETT: Hansson.

3 BY MR. PADGETT:

4 Q And you reference Hansson 1990, right?

5 A Yes.

6 (Exhibit No. 37 was marked for

7 identification.)

8 BY MR. PADGETT:

9 Q Doctor, this is 37. Dr. Louie, I'm

10 handing you what's been marked as Exhibit 37. Is

11 this the Hansson 1990 article you were referring

12 to earlier?

13 A Yes.

14 Q And in this study the authors -- Warner

15 isn't on this study, right?

16 A But Warner and Hansson published the

17 Warner paper.

18 Q Okay. In this study the authors probed

19 for CYP2E1 in the adult rat brain using an

20 antibody against CYP2E1. Is that right?

21 A They used a -- yes.

22 Q Okay. And they were able to detect a

23 signal; is that right?

24 A The signal is pretty strong.

25 Q Okay. But there was no quantification

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1 of that signal performed, was there, in the study?

2 A Yeah, so cytochrome P450 IIE1 is

3 localized in certain cells. So --

4 Q And it's -- so it's a -- it's a site-

5 specific issue. You have to look at it by tissue

6 organ specifically, is the same true for GSH in

7 terms of the levels, right?

8 A Yes, glial cells are right adjacent to

9 nerve cells. So that's where it becomes much more

10 important, what we call regional proximal effects.

11 Q Okay. But -- I don't think that

12 answered my question.

13 There was no quantification of this

14 signal that you say was high performed in the

15 Hansson 1990 case to determine the levels of

16 CYP2E1 protein or mRNA levels, correct?

17 A But Warner says 1 to 5 percent. So

18 that's sort of giving me the same -- you know,

19 it's -- when it says 1 to 5 percent, you -- you

20 got to believe that.

21 Q Well, Warner didn't involve the --

22 analyzing CYP2E1, right?

23 A And this staining is very similar to

24 that of Warner.

25 Q Dr. Louie, you didn't answer my

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1 question. I asked you whether Warner involved

2 CYP2E1 specifically, and you responded that the

3 staining was -- in Hansson was similar.

4 Do you understand why I don't feel like

5 you answered my question?

6 A So can you rephrase the question so

7 that --

8 Q Okay. Did Warner 1988 look at CYP2E1

9 specifically?

10 A It looked at cytochrome P450.

11 Q Did Warner 1988 look at CYP2E1

12 specifically?

13 MR. ADAMS: Object to form.

14 THE WITNESS: They did. They call it

15 differently.

16 BY MR. PADGETT:

17 Q Where is that?

18 A That's in the antibodies.

19 Q What page are you looking at?

20 A 1059. So they looked at cytochrome

21 P450E at that time. That's how they refer to it.

22 Q Aren't there more than one cytochrome

23 450E?

24 A Predominantly is 2.

25 Q And was there a -- were the results

<p style="text-align: right;">Page 202</p> <p>1 specified for 450 -- P450E in Warner?</p> <p>2 A Warner --</p> <p>3 Q And if you don't know, that --</p> <p>4 A Yeah, I got to remember exactly what I</p> <p>5 read.</p> <p>6 Can you restate your question again? My</p> <p>7 apologies.</p> <p>8 Q What were the -- did you see results for</p> <p>9 what you're saying is P450E looked at, and that</p> <p>10 would include, according to you, CYP2E1, did they</p> <p>11 have results for P450E set forth quantitatively in</p> <p>12 Warner 1988?</p> <p>13 A Excuse me.</p> <p>14 Q In the brain.</p> <p>15 A So in page -- they didn't -- page 1063,</p> <p>16 left -- left column, paragraph 2, point A: "Most</p> <p>17 of the P450 in the brain consists of forms other</p> <p>18 than the P450b, e or c and d."</p> <p>19 So they did look at the selectivity.</p> <p>20 Q But didn't quantify it.</p> <p>21 A They did not quantify it.</p> <p>22 MR. ADAMS: Can we take a break? We've</p> <p>23 been going a little over an hour. Thanks.</p> <p>24 MR. PADGETT: Yeah.</p> <p>25 THE VIDEOGRAPHER: One moment. We are</p>	<p style="text-align: right;">Page 204</p> <p>1 THE WITNESS: Yes.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q You've reviewed it?</p> <p>4 A Mm-hmm.</p> <p>5 (Exhibit No. 39 was marked for</p> <p>6 identification.)</p> <p>7 BY MR. PADGETT:</p> <p>8 Q Okay. And I'm going to hand you</p> <p>9 Brzezinski 1999 referenced in paragraph 39 of your</p> <p>10 report. Is that -- is that the Brzezinski 1999</p> <p>11 study, Exhibit 39?</p> <p>12 A Yes, I've seen this paper. That's the</p> <p>13 paper.</p> <p>14 (Exhibit No. 40 was marked for</p> <p>15 identification.)</p> <p>16 BY MR. PADGETT:</p> <p>17 Q And I'm going to hand you what's been</p> <p>18 marked as Exhibit 40, the Dutheil 2009 study, and</p> <p>19 ask you if you reviewed that study article.</p> <p>20 A (Peruses document.) No, I have not.</p> <p>21 Q So Exhibits 38 and 39 were referenced in</p> <p>22 Dr. McGill's report, but you have not reviewed of</p> <p>23 these three the Dutheil 2009 study.</p> <p>24 A I've reviewed your Exhibit 38.</p> <p>25 Q Mm-hmm.</p>
<p style="text-align: right;">Page 203</p> <p>1 going off the record at 3:14 p.m.</p> <p>2 (Recess.)</p> <p>3 THE VIDEOGRAPHER: We are going back on</p> <p>4 the video record at 3:29 p.m.</p> <p>5 BY MR. PADGETT:</p> <p>6 Q Dr. Louie, I noted that you referenced</p> <p>7 Brzezinski 1999. Paragraph 30 of your reply</p> <p>8 report, if you want to look at it.</p> <p>9 Is this the -- well, first of all, have</p> <p>10 you -- let me start with this. I'm going to hand</p> <p>11 you what's been marked as Exhibit 38.</p> <p>12 (Exhibit No. 38 was marked for</p> <p>13 identification.)</p> <p>14 BY MR. PADGETT:</p> <p>15 Q It's Boutelet-Bochan 1997. Are you</p> <p>16 familiar with that study?</p> <p>17 A It's part of the Brzezinski group,</p> <p>18 right?</p> <p>19 Q Are you familiar with that study, I</p> <p>20 guess is all I'm asking?</p> <p>21 MR. ADAMS: Real quick. Did you mark it</p> <p>22 as an exhibit, or are you just showing it to him</p> <p>23 for --</p> <p>24 MR. PADGETT: Yeah, I marked it as</p> <p>25 Exhibit 38. Oh, sorry. Apologies.</p>	<p style="text-align: right;">Page 205</p> <p>1 A And I guess Exhibit 39.</p> <p>2 I don't think I've seen your Exhibit 40.</p> <p>3 Q Okay. I want to talk to you about</p> <p>4 Exhibit 39, the Brzezinski study.</p> <p>5 Let me first go to page -- or paragraph</p> <p>6 17 of your reply --</p> <p>7 A 17?</p> <p>8 Q Yeah, of your reply report.</p> <p>9 A Okay.</p> <p>10 Q And there you -- you stated that</p> <p>11 Dr. McGill only -- in his report only cited</p> <p>12 studies about CYP2E1 expression. Right?</p> <p>13 A Where -- where are you seeing that? Is</p> <p>14 that paragraph 17, what line?</p> <p>15 Q Paragraph 30.</p> <p>16 A Oh.</p> <p>17 Q Do you see what I'm referring to there</p> <p>18 in paragraph 30?</p> <p>19 A My report, paragraph 30?</p> <p>20 Q Your reply report, yes.</p> <p>21 A Yes. I don't see where -- am I missing</p> <p>22 it, Dr. McGill's --</p> <p>23 Q I'm sorry. It's paragraph 17. You were</p> <p>24 in the right place. I apologize.</p> <p>25 The first sentence in paragraph 17,</p>

<p style="text-align: right;">Page 206</p> <p>1 quote: Studies cited by Dr. McGill in his report 2 did not specifically analyze CYP2E1 in the brain. 3 Instead, they highlighted the difference in 4 expression of CYP without specifying the isoforms. 5 Dr. McGill did cite the Brzezinski study 6 in his report. Do you recall that? 7 A Can you show me where exactly? 8 Q I believe it's in paragraph 32 to 39. 9 That's where he discusses it. And specifically 10 page 33 of his report. He cites Brzezinski. Do 11 you see that? 12 A I'm sorry. You said page 33? 13 Q 33, yes. 14 A I see it. 15 Q Okay. And Dr. McGill cites it and 16 examines CYP2E1 protein. Do you agree that 17 Brzezinski examined CYP2E1 protein levels? 18 A I do agree, but I will have to say this, 19 if you look at Brzezinski's data, it's different 20 because he says earlier that CYP2E1 is not there. 21 This is in embryo brain. 22 It shows you that -- in Figure 3, he 23 shows you the gestational period of human embryo, 24 and you see that there is bands there that shows 25 the cytochrome P450 IIE1. And they're not small.</p>	<p style="text-align: right;">Page 208</p> <p>1 A But -- should I answer the question? 2 Because you asked me that. It says fourfold 3 magnitude lower in prenatal brain compared to -- 4 very important -- adult rat liver. Adult. 5 So therefore, you got to make sure 6 you -- when you use those terminology, one of the 7 key elements is that the cell -- the brain of a 8 fetus is very small, so did they adjust for 9 protein levels. 10 Q And so for that reason, are you 11 discounting the finding that the CYP2E1 protein 12 found in the brain of Brzezinski was 150 less than 13 the adult rat liver? 14 A I'm just saying that, you know, the 15 enzyme is there, but the way he phrased it, that 16 it is almost undetectable, you see it in these -- 17 you see it in the picture here, it's detectable. 18 It's pretty high concentration, and enzymes don't 19 have to be in high concentrations because enzymes 20 are recyclable. Once you activate it, you can 21 get -- come back again. That's the definition of 22 enzyme. 23 Q If you can take a look at, I believe 24 it's, Exhibit 40. 25 THE REPORTER: 41 is the next number.</p>
<p style="text-align: right;">Page 207</p> <p>1 Q Are you saying that Dr. McGill stated 2 that there was no CYP2E1 in this study? 3 A He says it's a thousandfold less. 4 Q All right. And you're saying that this 5 only shows 150-fold less in the brain than the 6 liver. 7 A Yes. And more importantly, cytochrome 8 P450 is inducible -- the 2E1 is very inducible. 9 So I think it shows you that it's there within the 10 first trimester. And it shows in Figure 2, you 11 have specific activity. That means there is 12 enzymatic activity. 13 Q And if you look at page 1651 of 14 Brzezinski. 15 A 16 -- okay, I'm there. 16 Q In the left column, the end of the first 17 paragraph, it states that: "The CYP2E1 protein 18 specific activity was approximately four orders of 19 magnitude lower in prenatal human brain compared 20 to adult rat liver." 21 And my question is, do you agree that 22 the activity of CYP2E1 is important, not just its 23 presence? 24 A Yes. 25 Q Okay.</p>	<p style="text-align: right;">Page 209</p> <p>1 MR. PADGETT: I'm talking about Dutheil 2 2009. 3 You became the third person to spill 4 there. 5 THE WITNESS: This one? 6 BY MR. PADGETT: 7 Q Yes. 8 A Can I put these down? 9 Q Yes. 10 And can you -- and you have not reviewed 11 this study? 12 A Never read it. 13 Q Okay. And I take it then you have not 14 seen Table 2 at page 1530 either. 15 A I'm sorry? 16 Q You have not seen Table 2 at page 1530 17 of this study, right? 18 A Page -- Table 2, 1530. Oh, sorry. 19 No, I haven't seen this before. 20 Q Did you try to read all of the studies 21 cited in Dr. McGill's report before doing your 22 reply report? 23 MR. ADAMS: Object to form. 24 THE WITNESS: Did I read all his paper? 25 I think I responded to his criticism as -- because</p>

<p style="text-align: right;">Page 210</p> <p>1 you only gave me a week, so therefore, I think I</p> <p>2 picked and choosed the ones I needed to address</p> <p>3 quickly.</p> <p>4 BY MR. PADGETT:</p> <p>5 Q Okay. We talked about Kim. We talked</p> <p>6 about Posadas for your --</p> <p>7 A So you don't want this paper?</p> <p>8 Q You can put it down, yeah.</p> <p>9 Your earlier testimony that CYP2E1 is</p> <p>10 induced, other than Kim and Posadas, do you have</p> <p>11 any other studies showing that CYP2E1 is induced?</p> <p>12 A Inducible.</p> <p>13 Q Inducible.</p> <p>14 A So, Counselor, I don't know if you know,</p> <p>15 but it's actually in books, the cytochrome P450</p> <p>16 IIE1 is an inducible enzyme. You will read --</p> <p>17 almost any book that talks about metabolism, they</p> <p>18 will tell you that. It's inducible by steroids</p> <p>19 such as progesterone and estrogen, which is</p> <p>20 elevated during pregnancy.</p> <p>21 Q Any other studies other than Kim and</p> <p>22 Posadas that you rely on for the premise that</p> <p>23 CYP2E1 is inducible by acetaminophen?</p> <p>24 MR. ADAMS: Object to form.</p> <p>25 THE WITNESS: As I said to you, it is</p>	<p style="text-align: right;">Page 212</p> <p>1 pharmacologists.</p> <p>2 Q Kumar?</p> <p>3 A Kumar and Rahman are from the same</p> <p>4 group.</p> <p>5 Q And you're saying that Kumar 2017 shows</p> <p>6 that CYP2E1 is induced, increased by</p> <p>7 acetaminophen.</p> <p>8 A They state that. In 2019 -- I hope I</p> <p>9 pronounce it right -- Rahman actually has in their</p> <p>10 title.</p> <p>11 Q Rahman?</p> <p>12 A Yeah, R-H -- R-E-H-M-A-N (sic).</p> <p>13 (Exhibit No. 41 was marked for</p> <p>14 identification.)</p> <p>15 BY MR. PADGETT:</p> <p>16 Q If you turn -- well, sorry.</p> <p>17 I'm going to hand you what's been marked</p> <p>18 as Exhibit No. 41, which is the Kim study that you</p> <p>19 were talking about earlier.</p> <p>20 This study is about rats treated</p> <p>21 intraperitoneally with acetaminophen at 500</p> <p>22 milligrams per kilogram, and then 18 hours after</p> <p>23 the initial treatment, treated with 500 milligrams</p> <p>24 per kilograms or 1,000 milligrams per kilogram.</p> <p>25 Correct?</p>
<p style="text-align: right;">Page 211</p> <p>1 established. Any pharmacologist knows this. And</p> <p>2 there are so many papers that suggest the</p> <p>3 cytochrome P450 IIE1 is not only inducible by</p> <p>4 acetaminophen, alcohol, progesterone, estrogen.</p> <p>5 So I think that that's something that you don't</p> <p>6 want to -- to discuss.</p> <p>7 BY MR. PADGETT:</p> <p>8 Q Dr. Louie, if you could listen to my</p> <p>9 question, and very specifically.</p> <p>10 Are you aware of any other studies other</p> <p>11 than Kim and Posadas that show the inducibility of</p> <p>12 CYP2E1 by acetaminophen?</p> <p>13 MR. ADAMS: Object to form.</p> <p>14 THE WITNESS: I do.</p> <p>15 BY MR. PADGETT:</p> <p>16 Q What studies?</p> <p>17 A If I look at Kumar et al., and if you</p> <p>18 look at -- better yet, my report on 11 -- page 11</p> <p>19 of Rahman et al. shows that plasma exosome</p> <p>20 exacerbated by alcohol and acetaminophen induce</p> <p>21 toxicities. That's in 2019.</p> <p>22 Q Induced toxicities. I'm asking induce</p> <p>23 an increase in CYP2E1. That's my question.</p> <p>24 A If you read that paper, that's what it</p> <p>25 says, it's inducible. And those two guys are</p>	<p style="text-align: right;">Page 213</p> <p>1 A That's correct.</p> <p>2 Q Okay. And this study looked at rat</p> <p>3 livers, not --</p> <p>4 A Wait, wait, wait. I'm sorry, that's</p> <p>5 incorrect. It's two doses of 500 milligram per</p> <p>6 kilogram -- oh, I see. You're right. You're</p> <p>7 right. Correct.</p> <p>8 Q One was 500, and then some rats got 500</p> <p>9 more and some got 1,000 milligrams per kilogram,</p> <p>10 right?</p> <p>11 A Correct.</p> <p>12 Q Okay. And you didn't respond to this</p> <p>13 question. Do you agree that this looked at rat</p> <p>14 livers, not human brains?</p> <p>15 A I do.</p> <p>16 Q Okay. And we talked earlier that doses</p> <p>17 of 500 milligrams per kilogram or above are</p> <p>18 hepatotoxic, based on your own testimony and work</p> <p>19 with the FDA; is that right?</p> <p>20 A If I remember correctly how I stated to</p> <p>21 you, that 500 milligrams per kilogram, it can do</p> <p>22 that.</p> <p>23 Q Okay.</p> <p>24 A But -- let me finish -- but in this</p> <p>25 study the 500 milligrams per kilogram, the first</p>

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1 dose, and if you look at Table 1, the AST, the ALT
 2 were all within normal limits as compared to zero.
 3 So in this situation it was not hepatotoxic.
 4 But when you gave the second dose, you
 5 see that it goes from 85 to 224, and that was
 6 statistically significant. That's just two doses.
 7 Now, when you and I were talking about
 8 the rat, I said 500 to 1,000. You picked the
 9 lower end. Because 1,000 milligrams per kilogram
 10 in rats, that's hepatotoxic. 500 is marginal.
 11 And I think I said that to you.
 12 Q Are -- do you have any understanding as
 13 to whether rats are particularly resistant to
 14 acetaminophen, at least as far as hepatotoxicity
 15 is concerned?
 16 A According to Dr. McGill, that's what he
 17 said.
 18 Q Okay.
 19 A And he used 500 to 1,000.
 20 (Exhibit No. 42 was marked for
 21 identification.)
 22 BY MR. PADGETT:
 23 Q I'm going to show you what's been marked
 24 as Exhibit 42. Is that the Posadas 2010 study you
 25 were talking about earlier?

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1 A Yes, it is.
 2 Q Sorry to do this to you, but could you
 3 back up to the Kim article again.
 4 A Okay, go back to Kim.
 5 Q Yes.
 6 You indicated that that study showed a
 7 tenfold inducement of CYP2E1. Can you tell me
 8 where it shows that?
 9 A So you see Figure 2?
 10 Q Mm-hmm. Is that A -- A and B?
 11 A Mm-hmm. So you could see that the
 12 milligram there goes from 1 to 5. I think there
 13 is another one somewhere. I think it's -- oh,
 14 that's the Posadas.
 15 So the 2E1, you see the levels of
 16 control versus after -- sorry -- A, control, and
 17 under the line, that's the control compared to
 18 that after APAP.
 19 Q You're saying the white is a control and
 20 the black --
 21 A Oh, no, no, no. The low --
 22 Q Oh, you're talking about the staining at
 23 Figure 1 -- or at Figure 2A?
 24 A Figure 2A, you see here the control is
 25 pretty level. And then when you treat it with --

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1 with acetaminophen, notice it goes up in the
 2 cytochrome P450 IIE1 as well as cytochrome P450
 3 1A.
 4 Q Okay. From Figure 2A, where do you get
 5 the tenfold increase?
 6 A If you look further down, that's the
 7 quantification.
 8 Q And that is micromole per minimum 8 --
 9 A It's minute per --
 10 Q -- minute milligram per protein. Okay.
 11 A Yeah.
 12 Q And I'm looking at PNP, and that looks
 13 like the control is about 1.0, and the
 14 acetaminophen, the black box, was under 2.0,
 15 correct?
 16 A The black box of acetaminophen is under
 17 2.0.
 18 Q Okay. And that's not ten times, right?
 19 A Well, that's induced.
 20 Q That's not ten times induced.
 21 A No, no.
 22 Q Okay. PNA shows about 1.0 for the
 23 control, and a little bit less for -- than PNP for
 24 significant, and that is not ten times inducement,
 25 right?

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1 A Okay. Sorry, I was distracted.
 2 Q Do you agree that PNA is not ten times
 3 inducement, right?
 4 A It's the AM.
 5 Q You're saying it's the AM, and the AM
 6 looks like it's about -- a little above 3.5, and
 7 the acetaminophen is a little bit above 4.0. How
 8 is that ten times?
 9 MR. ADAMS: Object to form.
 10 THE WITNESS: (Peruses document.)
 11 Okay. I concede that.
 12 BY MR. PADGETT:
 13 Q Okay. AM is less than two times
 14 inducement.
 15 A That's after one dose.
 16 Q After one dose. Okay.
 17 A Yeah. And so Posadas -- right, so you
 18 get to see that there's other studies that show
 19 that.
 20 Q Okay. Let's move on to Posadas. I
 21 believe that's -- sorry, what exhibit is that?
 22 MS. KAPKE: 42.
 23 MR. PADGETT: 42? Got it.
 24 BY MR. PADGETT:
 25 Q I think -- look at the abstract there

<p style="text-align: right;">Page 218</p> <p>1 for Posadas. It states: "We have found that 2 acetaminophen causes concentration dependent 3 neuronal death in vitro at concentrations 1 and 4 2 millimolar that are reached in human plasma 5 during acetaminophen overdose." Correct? 6 A And you can read further on that are 7 also reached in the CSF of rats for three hours. 8 Q What is CSF? 9 A So if you read further on, and also 10 reached -- that's the following -- the next part 11 of the sentence: "... and that also reach in the 12 CSF," cerebral spinal fluid, "of rats for three 13 hours following intraperitoneal injections of 14 acetaminophen dose, 250 and 500 milligrams, that 15 are below those that are required to induce acute 16 hepatic failure in rats." 17 Q Okay. And concentration levels of 1 18 and 2 millimolar are not equivalent to 19 concentrations you would see in humans after a 20 therapeutic dose, correct? 21 A You even said that Dr. McGill said that 22 it -- that rats are resistant. So in this model, 23 you have to realize they're resistant, so 24 therefore you're going to have to use higher 25 concentrations.</p>	<p style="text-align: right;">Page 220</p> <p>1 stated that human equivalent dose -- therapeutic 2 dose for rats, he identified it at 150 to 200 3 milligrams per kilogram? 4 MR. ADAMS: Object to form. 5 THE WITNESS: Can you say that again? 6 BY MR. PADGETT: 7 Q You wouldn't know if you didn't read 8 Dr. Cabrera's report that he stated that -- I 9 believe it was page 34 of his report -- that the 10 human equivalent therapeutic dose for rats is 150 11 to 200 milligrams per kilogram. 12 MR. ADAMS: Object to form. 13 THE WITNESS: I didn't see his report. 14 I can -- I have no comments on that. 15 But as -- as Dr. McGill, I read his, and 16 I assume that he's one of the experts that you're 17 using. So he's opining that it takes 500 to 1 18 gram per kilogram in rats to cause these issues. 19 So I'm using the same guidance that he's 20 giving me, and I'm using this paper, and it shows 21 you that there's neuronal issues. And in 22 particular, neuronal toxicity because they said 23 neuronal death. 24 BY MR. PADGETT: 25 Q Is it your opinion that 500 milligrams</p>
<p style="text-align: right;">Page 219</p> <p>1 Q And the 1 and 2 millimolar are based on 2 use of 250 milligrams per kilogram and 500 3 milligram per kilogram via injections in vitro; is 4 that right? 5 A No, that's in medium, and so they added 6 that. But what is very key is that they said that 7 in animals, and I think I stated that in my 8 report, that it -- not just 500, but that they 9 used 250 and 500 milligrams, and that's below 10 liver toxic doses. 11 They were able to do several things. 12 They were able to show that acetaminophen also 13 increased both neuronal cytochrome P450 isoforms, 14 2E1. 15 Let's see, let me make sure I get this 16 right. I got a little depth perception issue. 17 Sorry. 18 "... enzymatic activity and protein 19 levels as determined by Western blot, leading to 20 neuronal death through mitochondrial-mediated 21 mechanisms that involve cytochrome c release and 22 caspase 3 activation." 23 Q Did you read Dr. Cabrera's report? 24 A No, I didn't. 25 Q So you are not aware if Dr. Cabrera</p>	<p style="text-align: right;">Page 221</p> <p>1 per kilogram in a rat is equivalent to a 2 therapeutic dose in a human? 3 A It doesn't matter, because in this case 4 they're looking at it in actual resistant model. 5 You even said that, and I'm just going by what you 6 said, and making sure that we are always in the 7 same street, that we're talking about the same 8 thing. 9 If 500 milligrams per kilogram is -- is 10 not -- that the rat is resistant, then we have to 11 agree that in this model it shows you that. 12 Q Is -- are you aware of whether the rat 13 is resistant to acetaminophen similarly in the 14 brain as it is in the liver? 15 A It doesn't matter, because we already 16 agree that this is subhepatic toxic doses. 17 And in fact, to add this, they didn't 18 just use 500, they used 250, which is half of 19 that. So we have to agree that that's less than 20 hepatic dosing, and yet they get the same effects 21 in the brain. 22 Q I'm asking you a specific question. Is 23 it your opinion that 500 milligrams per kilogram 24 is a therapeutic dose in a rat equivalent to 25 the therapeutic -- equivalent to a therapeutic --</p>

<p style="text-align: right;">Page 222</p> <p>1 strike that.</p> <p>2 Is it your opinion that 500 milligrams</p> <p>3 per kilogram dose in a rat is equivalent to a</p> <p>4 therapeutic dose in a human?</p> <p>5 MR. ADAMS: Object to form.</p> <p>6 THE WITNESS: It's kind of funny because</p> <p>7 I never give rat Tylenol for treating their</p> <p>8 headaches. So that's -- that's -- to me, that's</p> <p>9 kind of like -- I'm not sure I understand that.</p> <p>10 But you're -- you're saying a subhepatic</p> <p>11 toxic dose -- 500 milligrams per kilogram, is that</p> <p>12 a toxic dose? It could be.</p> <p>13 But it -- in this paper it says they use</p> <p>14 250. It's half of that. So as a pharmacologist,</p> <p>15 this is not going to be toxic to the liver, but</p> <p>16 yet we see some effects in the brain.</p> <p>17 BY MR. PADGETT:</p> <p>18 Q And this is measured by something called</p> <p>19 TUNEL. What is TUNEL?</p> <p>20 A TUNEL is a test to measure cellular</p> <p>21 apoptosis. That means cell death. So if it's</p> <p>22 TUNEL positive, you're getting cellular death.</p> <p>23 Q Are you aware of any human studies at</p> <p>24 therapeutic doses showing neuronal cell death in</p> <p>25 humans?</p>	<p style="text-align: right;">Page 224</p> <p>1 Q It said: Doses ranging from 350 to</p> <p>2 3,000 milligrams per kilogram are used to cause</p> <p>3 liver injury or liver failure in rodent studies.</p> <p>4 MR. ADAMS: Object to form.</p> <p>5 THE WITNESS: Well, it's hard for me to</p> <p>6 understand which rodent, because there's more than</p> <p>7 one rodent. You have mice, rats, hamsters, and</p> <p>8 guinea pigs. So I don't know what he's referring</p> <p>9 to.</p> <p>10 BY MR. PADGETT:</p> <p>11 Q Page 23 of your reply report,</p> <p>12 paragraph 20 -- 49 -- paragraph 49, if you want to</p> <p>13 look at it -- you criticize Dr. Powell for his</p> <p>14 position that the Posadas study's use of high</p> <p>15 acetaminophen concentrations makes it far removed</p> <p>16 from the real-life scenario of human fetus exposed</p> <p>17 to acetaminophen in utero.</p> <p>18 A I'm sorry, I'm not there yet.</p> <p>19 Q Okay.</p> <p>20 A (Peruses document.)</p> <p>21 Q Do you see that?</p> <p>22 A Yes, I see that.</p> <p>23 Q Okay. Posadas did not investigate fetal</p> <p>24 exposure in rodents, correct?</p> <p>25 A No, but he used subhepatic toxic levels.</p>
<p style="text-align: right;">Page 223</p> <p>1 A There's two problems with that. Number</p> <p>2 one, could you do the study and get away with it?</p> <p>3 Okay.</p> <p>4 But the second thing is Jetton et al.</p> <p>5 shows you that they have therapeutic doses, and</p> <p>6 they show apoptosis and hepatotoxic effects at</p> <p>7 1 gram four times a day. So that's a therapeutic</p> <p>8 dose.</p> <p>9 Q Are you aware of any human studies</p> <p>10 showing neuronal cell death at therapeutic doses</p> <p>11 of acetaminophen?</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 THE WITNESS: I already told you that it</p> <p>14 would not be a good idea to know that if it's</p> <p>15 toxic, you want to test that in humans.</p> <p>16 BY MR. PADGETT:</p> <p>17 Q Did you -- you said earlier you reviewed</p> <p>18 Dr. Pearson's report?</p> <p>19 A I brief -- looked through it briefly,</p> <p>20 yes.</p> <p>21 Q Do you remember page 76 of his report</p> <p>22 that he stated that, quote: Doses ranging from</p> <p>23 350 to 3,000 milligrams per kilogram are used to</p> <p>24 cause liver injury or liver failure in rodents?</p> <p>25 A Sorry, I didn't catch the last one.</p>	<p style="text-align: right;">Page 225</p> <p>1 So Dr. Powell didn't get it here. He's not a</p> <p>2 pharmacologist. He's a psychiatrist who does</p> <p>3 research in ADHD/ASD, and I don't think he --</p> <p>4 that's -- unfortunately, I don't -- I mean, he</p> <p>5 said Posadas doesn't make sense, but it shows</p> <p>6 neuronal toxicity.</p> <p>7 Q Dr. Powell is a neuroscientist. He's</p> <p>8 not a psychiatrist, but I'll --</p> <p>9 Do in vitro studies have absorption,</p> <p>10 distribution, metabolism or elimination processes</p> <p>11 in place?</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 THE WITNESS: It depends how you set it</p> <p>14 up. It could be. In my lab we do it.</p> <p>15 BY MR. PADGETT:</p> <p>16 Q For in vitro studies?</p> <p>17 A Sure.</p> <p>18 Q You replicate absorption, distribution,</p> <p>19 metabolism and elimination processes?</p> <p>20 A Yes. It's a system called hollow fiber</p> <p>21 system.</p> <p>22 Q Okay. And did Posadas do that?</p> <p>23 A He didn't -- I don't know if it's a he</p> <p>24 or she.</p> <p>25 Q She/he.</p>

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1 A Yeah, Posadas, I don't think did that.

2 Q The cultured cells treated in vitro in

3 Posadas were exposed to acetaminophen at these

4 concentrations of 1 to 2 millimolar for 18 to 24

5 hours straight, correct?

6 A Correct.

7 Q Okay. Do you agree that that amount of

8 time that this dose for concentration is

9 inconsistent with rapid clearance and short

10 life -- half-life of acetaminophen in the body?

11 MR. ADAMS: Object to form.

12 THE WITNESS: To be fair, we all concede

13 that acetaminophen is not toxic. Correct?

14 So if that's the case, it has to be --

15 it has to be converted to NAPQI, right? Or you

16 guys call it NAPQI. So that tells you that

17 neuronal cells make cytochrome P450 IIE1 at

18 sufficient levels to kill it.

19 So therefore, it shows you that the

20 neuronal cells express cytochrome P450 IIE1. I

21 think I said that in my report. And so therefore,

22 you need -- and if you use lower concentrations

23 and put it in longer, let's say 48 hours, you may

24 have the same effects.

25 BY MR. PADGETT:

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1 Q At page 52 of your amended report,

2 your -- the other one before you --

3 A Amended.

4 Q -- you state that --

5 A Can you let me get there?

6 Q Sure.

7 A Yes.

8 Q You note that the -- at page 52, that 66

9 to 198 micromolars, the peak blood or plasma

10 concentrations seen in humans from therapeutic

11 dosing of acetaminophen; is that right?

12 A Can you say it again so I remember the

13 units? Because I didn't catch the units.

14 Q Sure. I'm going to go to page 52 of

15 your report.

16 Okay. At the end of paragraph 130 in

17 your amended report of June 21, you say that

18 1 gram of acetaminophen can produce peak blood

19 plasma concentration of 66 to 198 micromolar,

20 right?

21 A 52 -- page 52?

22 Q Yes. Paragraph 130, the last sentence.

23 A I must be reading it differently. 130

24 -- oh, 130.

25 Q Yes.

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1 A I'm looking at 131. Sure. Yes.

2 Q Okay. And do you agree that that is

3 five times if we're talking 198 to 30 times if

4 we're talking 66 micromolars less than 1

5 millimolar or 2 millimolar -- I'm sorry -- yes, 1

6 millimolar or 2 millimolar? Do you agree with

7 that?

8 A I agree with that.

9 Q Okay.

10 A But I want to make sure you understood

11 that I said in paragraph 131 that after one hour

12 of 0.1 millimolar, which is 100 micromolar, the

13 GSH level dropped 15 percent as compared to GSH

14 level in untreated.

15 That's 131 -- one, two, three -- line 3.

16 And in fact, in two hours it was greater than 20

17 percent.

18 Q If you would turn back to Posadas. Turn

19 to page 6, Figure 5A.

20 Would you agree that incubating cultured

21 rat neurons with 1 micromolar of acetaminophen

22 decreased glutathione, GSH, by less than 25

23 percent and 2 millimolar decreased it by

24 approximately 50 percent?

25 A That's a lot.

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1 Q But GSH was still present even at

2 concentrations ranging from 5 to 30 times the peak

3 concentrations in humans at therapeutic doses,

4 right?

5 A So you're looking at Figure 5A -- 5,

6 right, A?

7 Q Mm-hmm. Yes.

8 A And it says, "Percentage GST." That's

9 why I'm a little confused.

10 So is GST glutathione levels? I want to

11 make sure I got that right. It's percentage of

12 glutathione levels, correct?

13 Q Correct.

14 A So -- so that's a, in fact,

15 statistically significant drop of glutathione. So

16 your point was that it was -- this is high

17 concentrations.

18 Q Yes.

19 A Yes, it is high concentrations.

20 But it also shows that the cytochrome

21 P450 IIE1 is expressed in neurons. Because

22 without that, you can't make NAPQI, and therefore

23 deplete GSH.

24 Q GSH doesn't conjugate other -- anything

25 other than NAPQI?

<p style="text-align: right;">Page 230</p> <p>1 A Not in this study, because your vehicle</p> <p>2 is 100 percent. This is in comparison to vehicle,</p> <p>3 you see that the drop occurs. So this is a</p> <p>4 percentage of vehicle.</p> <p>5 So therefore, there could be, but now</p> <p>6 you had acetaminophen, and that's the only</p> <p>7 difference between the two. That's why cellular</p> <p>8 studies are a causal relationship, whereas other</p> <p>9 studies are different because there's -- there is</p> <p>10 only a few parameters that are changed there.</p> <p>11 Q And it -- is it your opinion that these</p> <p>12 drops were so -- were sufficient to not be able to</p> <p>13 conjugate any NAPQI that may have been formed?</p> <p>14 A So in your next slide -- I mean, in B,</p> <p>15 A1 looks like you start to increase your reactive</p> <p>16 oxygen species, which should tell you that now</p> <p>17 we're having cascade effects. And this is what</p> <p>18 kills the cells is the reactive oxygen species.</p> <p>19 Q And this is in vitro, and they're in</p> <p>20 there at these concentrations for 18 to 24 hours,</p> <p>21 right?</p> <p>22 A And they -- they compare that in vitro,</p> <p>23 and then inject it into rats showing in vivo</p> <p>24 effects, which you should then at that point say,</p> <p>25 Ah, it may be 1 millimolar high, but at</p>	<p style="text-align: right;">Page 232</p> <p>1 A Take a needle, stick it in the stomach.</p> <p>2 Q Okay. And do you agree that IP</p> <p>3 injection bypasses first pass metabolism?</p> <p>4 A That's not fair, because first pass</p> <p>5 metabolism is only one time. Once it gets in the</p> <p>6 blood, it will go back to the liver.</p> <p>7 So as a pharmacologist, you get these</p> <p>8 guys who are making these comments, and they're</p> <p>9 not pharmacologists. First pass effect doesn't</p> <p>10 mean it passes hepatic metabolism. So that's --</p> <p>11 so you know, sub-Q and oral, we use them side by</p> <p>12 side.</p> <p>13 Q Is IP injection stressful for rats?</p> <p>14 A Sure. So is oral.</p> <p>15 Q Okay. Gavage studies are stressful oral</p> <p>16 dosing, right?</p> <p>17 A Gavage.</p> <p>18 Q Gavage. Okay.</p> <p>19 But putting it in drinking water for</p> <p>20 mice or rats is not stressful like gavage or IP</p> <p>21 injections. Agree?</p> <p>22 A Disagree. Acetaminophen is very bitter.</p> <p>23 Have you ever tasted your -- your child's liquid</p> <p>24 acetaminophen? It's super bitter.</p> <p>25 Q How -- have you measured whether mice or</p>
<p style="text-align: right;">Page 231</p> <p>1 sub-hepatotoxic doses, you can cause neuronal</p> <p>2 effects.</p> <p>3 Q And you mentioned you're now</p> <p>4 transitioning to the in vivo experiments with the</p> <p>5 adult model animals in the Posadas study, right?</p> <p>6 A That's a -- yeah.</p> <p>7 Q Okay. Are you aware that Dr. Pearson</p> <p>8 excluded the in vivo portion of this study from</p> <p>9 his review as not relevant due to it relating to</p> <p>10 adult animals?</p> <p>11 MR. ADAMS: Object to form.</p> <p>12 BY MR. PADGETT:</p> <p>13 Q In footnote 7 of his report.</p> <p>14 MR. ADAMS: Object to form.</p> <p>15 THE WITNESS: You had to go down that</p> <p>16 far -- no, I don't think I read his -- his</p> <p>17 footnote, so I'm not aware.</p> <p>18 BY MR. PADGETT:</p> <p>19 Q All right. And in the in vito -- in</p> <p>20 vivo experiments, the rats were treated by IP --</p> <p>21 intraperitoneal injection to the 250 and the 500,</p> <p>22 right?</p> <p>23 A That's what the method says.</p> <p>24 Q Okay. Can you explain what</p> <p>25 intraperitoneal injection is?</p>	<p style="text-align: right;">Page 233</p> <p>1 rats view acetaminophen as bitter tasting as a</p> <p>2 part of studies involving oral dosing?</p> <p>3 A We have. So what we -- to the point</p> <p>4 that we no longer put it in water, we put it in</p> <p>5 their -- in their -- in these what they call gels,</p> <p>6 which are flavored, so it hides the taste.</p> <p>7 Q Do you agree that IP injection in adult</p> <p>8 rats does not replicate the exposures that would</p> <p>9 be expected for a fetus via mother due to</p> <p>10 gestational exposure?</p> <p>11 A Going back, injection in the</p> <p>12 intraperitoneal is similar to if you took the</p> <p>13 needle and gave insulin into your stomach. So</p> <p>14 the -- the rats do get used to it.</p> <p>15 Q And 1 millimolar is how many</p> <p>16 micromolars?</p> <p>17 A It's a thousand.</p> <p>18 Q Okay. For the tenfold induction, you're</p> <p>19 relying on the in vitro part of the Posadas study</p> <p>20 on rat cortical cells?</p> <p>21 MR. ADAMS: Object to form.</p> <p>22 BY MR. PADGETT:</p> <p>23 Q Do you agree?</p> <p>24 A I'm not sure where you're referring to.</p> <p>25 Is there a figure you can --</p>

<p style="text-align: right;">Page 234</p> <p>1 Q Are you relying on both the in vitro</p> <p>2 part of Posadas and the in vivo part of Posadas</p> <p>3 for this tenfold induction?</p> <p>4 A Figure 6 shows you that.</p> <p>5 Q Which for CYP2E1, Figure 6B, is that</p> <p>6 what you're talking about?</p> <p>7 A Correct.</p> <p>8 Q And you are -- and is the black bar the</p> <p>9 control?</p> <p>10 A The vehicle.</p> <p>11 Q The vehicle?</p> <p>12 A Yes.</p> <p>13 Q And is there anything else that you are</p> <p>14 relying on other than this Figure 6B --</p> <p>15 A Well --</p> <p>16 Q -- for the ten part -- tenfold increase?</p> <p>17 MR. ADAMS: Object to form.</p> <p>18 THE WITNESS: So as you look at that,</p> <p>19 that's the ratio. Looking at vehicle, 1.5 to --</p> <p>20 close to hour 6 is close to 1.5. So it looks</p> <p>21 pretty close to one-point -- tenfold its protein</p> <p>22 levels.</p> <p>23 BY MR. PADGETT:</p> <p>24 Q Okay. So that is your basis for the</p> <p>25 tenfold increase. Is there anything else in terms</p>	<p style="text-align: right;">Page 236</p> <p>1 there was detectable cytochrome P450 IIE1 in fetal</p> <p>2 brains, human fetal brains.</p> <p>3 Q You come up with this calculation in</p> <p>4 your reply report that states that based on the</p> <p>5 1.5 -- 1 to 5 percent number in Warner 1988,</p> <p>6 that's based on CYP450 broadly, right?</p> <p>7 A Yes.</p> <p>8 Q And you use the top number there of</p> <p>9 5 percent, right?</p> <p>10 A As did most of your experts. I'm just</p> <p>11 using -- I'm going -- I'm doing what your experts</p> <p>12 do and what I do, yes, absolutely. We use the</p> <p>13 higher level.</p> <p>14 Q The higher level of 5 percent, and</p> <p>15 that's for not CYP2E1 specifically, but CYP450</p> <p>16 broadly, right?</p> <p>17 A But I think Brzezinski shows you that</p> <p>18 2E1 does have that expression.</p> <p>19 Q My question is the 5 -- 1 to 5 percent</p> <p>20 number, you used the 5 percent number, and that's</p> <p>21 based on CYP450 broadly as a whole from Warner</p> <p>22 1988, correct?</p> <p>23 MR. ADAMS: Object to form.</p> <p>24 THE WITNESS: Correct. And I reminded</p> <p>25 you in -- even in my original amended report, it</p>
<p style="text-align: right;">Page 235</p> <p>1 of numbers in Posadas that show that, that state</p> <p>2 the tenfold increase?</p> <p>3 A So you look at their NA, it does the</p> <p>4 same thing, right? This is looking at cytochrome</p> <p>5 P450 biological activity. It's pretty similar.</p> <p>6 It's -- it may not -- it's close to 10, so I</p> <p>7 approximate to 10.</p> <p>8 Q The vehicle shows it's almost halfway to</p> <p>9 0.5, and the A2 shows it's just above 1.0; is that</p> <p>10 right?</p> <p>11 A Okay, it's fivefold, still with one</p> <p>12 treatment. So remember I keep saying it's not</p> <p>13 just one dose, it's many treatments that makes</p> <p>14 this.</p> <p>15 Q And this is at 1 millimolar -- and what</p> <p>16 are -- in Figure 6A, what are the concentrations</p> <p>17 here reflected? Or the doses?</p> <p>18 A 6A concentrations -- 0.5, 1 and 2</p> <p>19 millimoles.</p> <p>20 Q Okay. The 1 to 5 percent number in</p> <p>21 Warner 1988 that you discuss in your reply report,</p> <p>22 is that based on CYP2E1 specifically or all CYP450</p> <p>23 enzymes looked at in that study?</p> <p>24 A I think you and I already agreed that it</p> <p>25 was generalized, but Brzezinski shows you that</p>	<p style="text-align: right;">Page 237</p> <p>1 doesn't say CYP2E1 in the diagram. It says CYP.</p> <p>2 And there's a reason for that because there's data</p> <p>3 that suggests 2E1 is important. 3A is important.</p> <p>4 1A is important.</p> <p>5 So I cannot differentiate which one, but</p> <p>6 to be broadly speaking, all of them can convert</p> <p>7 acetaminophen to NAPQI.</p> <p>8 BY MR. PADGETT:</p> <p>9 Q Okay. If you could turn to paragraph 14</p> <p>10 of your reply report, please.</p> <p>11 You state -- and this is towards the</p> <p>12 bottom of the page on line -- up on page 6 in</p> <p>13 paragraph 14 -- Warner --</p> <p>14 A Wait, wait, you said 14. Now you said</p> <p>15 page 6. Which is it?</p> <p>16 Q Paragraph 14, page 6.</p> <p>17 A Okay. Forgive me. Okay.</p> <p>18 Q Okay. "Warner et al. reports that</p> <p>19 CYP2E1 protein levels range from 1 to 5 percent</p> <p>20 when compared to the liver, which is in contrast</p> <p>21 to Dr. McGill's assertion" -- you've got a</p> <p>22 footnote 5 and that specifically refers to Warner</p> <p>23 1988, right?</p> <p>24 A Correct.</p> <p>25 Q Okay. Warner 1988 did not specifically</p>

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1 find CYP2E1 protein levels ranging from 1 to 5
 2 percent when compared to the liver. It was 1 to 5
 3 percent of CYP450 overall, right?
 4 A Fair enough. But the 2E1 was found
 5 elsewhere in that paper --
 6 Q And --
 7 A -- to be fair. I mean, if you're going
 8 to take it in isolation, I got to give you -- you
 9 know, if I said this in the classroom, I would get
 10 in so much trouble.
 11 Q Well -- and I think you mentioned
 12 Hansson -- was it Hansson?
 13 A Mm-hmm.
 14 Q -- as the follow-up to some of the same
 15 group, Hansson was a coauthor here.
 16 Did that show 1 to 5 percent CYP2E1
 17 levels compared to the liver in Hansson?
 18 A No, they didn't quantify it.
 19 Q Okay. It's a signal, right?
 20 A A signal, yeah. Yep.
 21 Q So Warner does not specifically find
 22 that CYP2E1 protein levels range from 1 to 5
 23 percent when compared to the liver. Agree?
 24 A That doesn't mean it doesn't exist. It
 25 doesn't mean it -- because Brzezinski shows you it

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1 exists. And Kim et al. shows it's inducible.
 2 Posadas shows you it's inducible. And in fact, I
 3 think the general -- if you look at books that
 4 work on cytochrome P450 IIE1 will tell you CYP2E1
 5 is inducible.
 6 Q Okay. You -- through your calculations
 7 that involve the 5 percent number based on Warner
 8 1988, which didn't address CYP2E1 in that fashion,
 9 and the inducement tenfold that you've -- you're
 10 relying on Posadas for that, correct?
 11 A Fair enough, Posadas.
 12 Q Okay. You conclude that 5.25 grams of
 13 acetaminophen is a threshold leading to neurotoxic
 14 effects after a single acetaminophen dose. Right?
 15 A I never said as a single -- oh, excuse
 16 me. Sorry. You're right.
 17 Q Okay.
 18 A Single acetaminophen dose, yes.
 19 Q Okay. That is well above the maximum
 20 total dosage allowed in one day for a human
 21 pursuant to the label for acetaminophen products.
 22 Do you agree?
 23 A It was. It is.
 24 Q Okay. And --
 25 A But --

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1 Q -- that's 5.25 times the maximum single
 2 dose -- therapeutic dose on the acetaminophen
 3 product labels. Agree?
 4 A To be careful, 1 gram four times a day
 5 is 4 -- is 4 grams, correct?
 6 Q Yes.
 7 A Okay. So you are 80 -- almost -- let's
 8 say 75 percent of 5.25. So you're reaching very
 9 close because of the cumulative dose, and when you
 10 start to use it more than once, it starts to
 11 induce. This is what -- the issue was
 12 inducibility was a very narrow inducibility study.
 13 They did it within 18 hours. What happens if it
 14 was seven days?
 15 Q Is what you just said, does that take
 16 into account the half-life of 30 -- or of 90 to
 17 180 minutes, 1.5 to three hours, of acetaminophen
 18 in the human body?
 19 A Does that take it into account?
 20 Q Yeah.
 21 A So you look at Rigobello, inject it into
 22 mice -- excuse me -- rats that were pregnant, then
 23 sure enough at low doses, 35 milligrams per
 24 kilogram, their pups had issues. Glutathione
 25 levels in the brain were different.

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1 So it sort of gives you that at -- below
 2 hepatotoxic doses, in pups or offsprings they had
 3 issues.
 4 Q I just want to make sure that we agree
 5 on the math here. 5.25 grams --
 6 A By the way -- oh, sorry.
 7 Q 5.25 grams in a single dose is 5.25
 8 times the maximum single dose for acetaminophen
 9 per the label. Agree?
 10 A I agree. But very importantly, this
 11 calculation looked at 70 percent depletion of
 12 glutathione in the liver. That's what Dr. McGill
 13 referenced. But in his own report, he said less
 14 is required.
 15 So I gave you the largest lead way. And
 16 I used the exact mathematics that he used in his
 17 report, which I believe came from Mitchell.
 18 And by the way, Mitchell also said
 19 cytochrome P450 IIE1 was inducible, and that was I
 20 believe in the 1990 -- '90s.
 21 MR. PADGETT: We've been going for a
 22 while. You want to take a break?
 23 MR. ADAMS: Yes, yeah. Let's get off
 24 the record.
 25 THE VIDEOGRAPHER: Going off the video

<p>1 record at 4:34 p.m. 2 (Recess.) 3 THE VIDEOGRAPHER: We are going back on 4 the video record at 4:55 p.m. 5 (Exhibit No. 43 was marked for 6 identification.) 7 BY MR. PADGETT: 8 Q Dr. Louie, I'm going to hand you what's 9 been marked as Exhibit 43. It's a study, 10 "Glutathione S-transferases and thiol 11 concentrations in embryonic and early fetal 12 tissues," Rajmakers, looks like, 2001. 13 I did not see this article on your list 14 of materials for your amended -- your initial 15 report. Did you review that article before 16 preparing your amended report? 17 A I don't believe I have. 18 Q Okay. Have you seen this article 19 before? 20 A I have not. 21 Q Okay. It's referenced in Dr. McGill's 22 report, specifically at page 41. And -- 23 A (Peruses document.) 24 Q As you are reviewing it, I would like to 25 specifically turn to Table 2.</p>	<p>Page 242</p> <p>1 right? 2 A This is looking at tissue, not blood 3 levels, right? 4 Q Correct. 5 A So it would be a lot higher in cells. 6 Q And in the embryo at eight weeks, 7 there's no brain tissue listed for GSH. Agree? 8 A It doesn't mean it doesn't exist, but 9 they don't list it. 10 Q Okay. And glutathione at 13 weeks, it 11 shows 26.2 nanomolar per milligram for GSH. 12 Right? 13 A I'm trying to look where the units are. 14 Q Well, its cysteine, homocysteine, 15 cysteinylglycine and glutathione. 16 A I see. So it's in A. So nanogram per 17 milligram of tissue. Okay. Okay. 18 Q Okay. But for the liver, it's 26.2 19 nanogram -- or nanomolar per milligram, right, for 20 GSH? 21 A Nanogram per milligram of tissue, yes. 22 Q Yes. And for brain, it's 80.1 nanomolar 23 per milligram for GSH. Do you see that? 24 A That's what it says there. 25 Q Okay. And that's -- so this showed that</p> <p>Page 244</p>
<p>1 A Table 2? 2 Q Yes, on page 2247. 3 Have you had an opportunity to -- to 4 review it a bit? 5 A Yeah, I did. 6 Q Okay. And in this study they looked at 7 glutathione S-transferases and thiol 8 concentrations in embryonic and early fetal 9 tissues in humans; is that right? 10 A I'm still reviewing. I'm sorry. That's 11 what the title says. 12 Q And if you look at Table 2, they looked 13 at eight weeks and 13 weeks, right? 14 A I'm looking at that right now. Eight 15 weeks and 13 weeks. Yes. 16 Q And this Table 2 is for cytosolic thiol 17 concentrations in embryonic and fetal organs, 18 correct? 19 A Slow down, because I -- 20 Q Yeah. 21 A This is the first time I've seen this. 22 Cytosolic -- okay, sorry -- 23 concentrations. I got to make sure I understand 24 what that means. 25 Q It included looking at glutathione,</p> <p>Page 243</p>	<p>1 the GSH was three times as high in the 13-week 2 fetus as the liver. Agree? 3 A Well, the way that Dr. McGill compared 4 it is very different. He gave total liver in 5 adult, and he compared that to a fetal brain. So 6 that's very important. 7 Here -- yeah, and what is also very odd 8 is that the adrenal gland at the highest level. 9 Q Why is that odd? 10 A Adrenal gland is very small, and no need 11 to be extremely high levels. 12 Q Are you questioning the findings of this 13 study? 14 A I'm just -- you look at week 8, it's 15 38.7, and then you go almost triple in week 13. 16 Just asking that question. 17 Q Yeah. In doing your reply report, 18 though, before signing that, you did not review 19 this study, even though it was in Dr. McGill's 20 report at page 41? 21 A This -- and this doesn't tell me how 22 many animals were done, correct? 23 Oh, this is humans. 24 Q Yes, this is a human study, correct? 25 A It looks like very few patient --</p> <p>Page 245</p>

<p style="text-align: right;">Page 246</p> <p>1 individuals were actually -- it doesn't tell me 2 how many fetuses. 3 Q Okay. 4 A So I'm -- how reputable if they don't 5 tell you the number. 6 (Exhibit No. 44 was marked for 7 identification.) 8 BY MR. PADGETT: 9 Q I'm going to hand you what's been marked 10 as Exhibit 44, Dr. Louie. 11 And earlier I think you mentioned the 12 Kumar 2017 study. Is that the Kumar 2017 study? 13 A Yes, I believe this is. 14 Q And I think it's paragraph 21 of your 15 reply report. 16 MR. PADGETT: Oh, Kara. Can you -- 17 sorry. 18 THE WITNESS: 25 -- paragraph 25? 19 BY MR. PADGETT: 20 Q Paragraph 21 of your reply report. You 21 stated that: "CYP2E1 expression is not limited to 22 tissues and/or organs but also found ubiquitously 23 in the blood, specifically in the plasmas in the 24 forms of exosomes." 25 Do you see that?</p>	<p style="text-align: right;">Page 248</p> <p>1 correctly have very few Ns. So I need to know 2 what the N is. N is the number of samples. I -- 3 Q At least based on the number of samples 4 in that study, brain GSH was three times liver GSH 5 at 13 weeks. 6 MR. ADAMS: Object to form. 7 BY MR. PADGETT: 8 Q Agree? 9 A It looks like one for each time point. 10 Q Back to Kumar 2017. Are you saying that 11 CYP2E1 in exosomes is somehow getting to the 12 brain? 13 A No. 14 Q Okay. 15 A I'm saying the exosomes in the blood, 16 like the liver, like the brain, can make NAPQI. 17 Q Okay. But we talked about earlier that 18 as far as GSH and CYP2E1, it's site-specific issue 19 as to effects. 20 MR. ADAMS: Object to form. 21 THE WITNESS: You're making an 22 assumption of one sample and you're assuming 23 that -- in fact, I don't like this paper for two 24 reasons. They use HPLC. In 2001, you could have 25 used LC-MS. So therefore, you could have</p>
<p style="text-align: right;">Page 247</p> <p>1 A I'm sorry. I didn't catch that. 2 Q You state that: "CYP2E1 expression is 3 not limited to tissues and/or organs but also 4 found ubiquitously in the blood -- in blood, 5 specifically in the plasmas in the form of 6 exosomes." 7 Do you see that? 8 A I see that. 9 Q Okay. Does the Kumar 2017 study in any 10 way suggest that exosomal CYP2E1 gets into the 11 fetal brain? 12 A It doesn't have to. Because it is 13 producing NAPQI in the blood, it can pass the 14 blood-brain barrier, it goes through the placenta 15 barrier, and then you -- you have to accommodate. 16 You have to have enough glutathione to mitigate 17 it. 18 This study is essentially telling you 19 that you have a different source of cytochrome 20 P450 IIE1. 21 Q And based on the Rajmakers study that 22 we just discussed, at least in 13-week-old fetuses 23 there's more GSH in the brain than in the liver, 24 right? 25 A The Rajmakers study, if I remember</p>	<p style="text-align: right;">Page 249</p> <p>1 glutathione or glutathione disulfate. 2 So therefore, he didn't differentiate 3 that, neither did he use -- let's see, did he 4 use -- I don't see him using dithiothreitol, which 5 keeps it as one. 6 BY MR. PADGETT: 7 Q Okay. My question was about the Kumar 8 2017 study, though, and the question is whether -- 9 does it show the CYP2E1 was getting into the fetal 10 brain through exosomes? 11 A So you made the comment, and I was 12 answering it that your glutathione in the brain in 13 this paper is just one sample. 14 Q Okay. 15 A Okay. Second, and I told you I had 16 issue with this because the method is not what 17 most people are now using, which is liquid 18 chromatography-mass spectrometry. 19 So having said that, and they didn't 20 tell me if it's glutathione SH or glutathione -- 21 let me finish -- GSSG. Because I know you can 22 talk. So therefore, they didn't separate them. 23 Q Okay. I'm asking you about Kumar 2017. 24 Are you saying that CYP2E1 exosomes 25 travel to and get into the fetal brain?</p>

<p style="text-align: right;">Page 250</p> <p>1 A I didn't say that. I said</p> <p>2 circulating -- imagine in the mother's blood and</p> <p>3 it's circulating down there, and there's</p> <p>4 acetaminophen getting down there, can make it and</p> <p>5 can pass through.</p> <p>6 Q So these exosomes with CYP2E1 wouldn't</p> <p>7 be reflected in brain toxicity in the -- in human</p> <p>8 fetuses.</p> <p>9 A I'm not sure what you just said.</p> <p>10 Q My question is -- so you point to the</p> <p>11 study as showing that the CYP2E1 is in exosomes in</p> <p>12 the blood, right?</p> <p>13 A Correct.</p> <p>14 Q Okay. And my question is -- and I think</p> <p>15 we've confirmed this -- Kumar does not address if</p> <p>16 CYP2E1 in exosomes get into the fetal brain --</p> <p>17 MR. ADAMS: Object to form.</p> <p>18 BY MR. PADGETT:</p> <p>19 Q -- right?</p> <p>20 MR. ADAMS: Object to form.</p> <p>21 THE WITNESS: I don't know if I agree</p> <p>22 with you, because I don't know the answer -- okay,</p> <p>23 I don't know the answer.</p> <p>24 But let's say it circulates. Can the</p> <p>25 cytochrome P450 in the blood in the presence of</p>	<p style="text-align: right;">Page 252</p> <p>1 The atlas to me -- I don't know if someone put it</p> <p>2 up there. How it's regulated. That's why I don't</p> <p>3 like web -- web databases. I want to see papers</p> <p>4 that allows me to download the raw data.</p> <p>5 Now, to be fair, I think Brzezinski and</p> <p>6 all shows cytochrome P450 in fetal brain. You</p> <p>7 agreed to that.</p> <p>8 Q I didn't agree to anything, Dr. Louie.</p> <p>9 A Well, the paper states that, okay?</p> <p>10 Q At levels higher or lower in the brain</p> <p>11 than in the liver, correct?</p> <p>12 A They didn't do milligram per milligram</p> <p>13 of tissue, which this paper did. And so -- but it</p> <p>14 shows you across not one sample but many samples</p> <p>15 that it's there.</p> <p>16 Q Did you read Dr. Baccarelli's report?</p> <p>17 A I'm not sure what you're asking for.</p> <p>18 Did I --</p> <p>19 Q I think you -- did -- yeah, you reviewed</p> <p>20 Dr. Baccarelli's report, and we confirmed that</p> <p>21 earlier, right?</p> <p>22 A Yeah.</p> <p>23 Q Were you aware of footnote 137 of his</p> <p>24 report, that he cites The Human Protein Atlas as a</p> <p>25 source?</p>
<p style="text-align: right;">Page 251</p> <p>1 acetaminophen, can it make NAPQI? The answer is</p> <p>2 yes.</p> <p>3 BY MR. PADGETT:</p> <p>4 Q In the brain, fetal brain?</p> <p>5 A No, no, no. You -- don't add -- I said</p> <p>6 in the blood, and the NAPQI can travel. If it's</p> <p>7 not neutralized, it can travel.</p> <p>8 Q And as it traveled, it may meet GSH in</p> <p>9 other places.</p> <p>10 A It may meet GSH. It could also make</p> <p>11 endothelial cells in the blood vessels or in the</p> <p>12 placenta, cause damages, and then therefore,</p> <p>13 things flow right through.</p> <p>14 Q But you're not talking about in the</p> <p>15 brain, right?</p> <p>16 A Once it gets into the placenta, it gets</p> <p>17 to the cord blood into the baby, and then it can</p> <p>18 get into the brain. Because acetaminophen gets</p> <p>19 into the blood, and it gets into the brain.</p> <p>20 Q And would that be captured in CYP2E1</p> <p>21 levels shown in, for example, The Human Protein</p> <p>22 Atlas and some of the other studies that we talked</p> <p>23 about -- about -- with regard to mRNA expression</p> <p>24 and CYP2E1 levels in the brain?</p> <p>25 A So there is discrepancy in your atlas.</p>	<p style="text-align: right;">Page 253</p> <p>1 A I will be honest with you, you're asking</p> <p>2 me to read footnotes. The answer is probably no.</p> <p>3 Q Okay.</p> <p>4 A Yeah.</p> <p>5 Q Are you -- are you indicate -- are you</p> <p>6 testifying today that you believe that the</p> <p>7 information on The Human Protein Atlas is</p> <p>8 unreliable?</p> <p>9 MR. ADAMS: Object to form.</p> <p>10 THE WITNESS: I don't know much of the</p> <p>11 Human Atlas as how it is paginated, who supports</p> <p>12 it, and if -- if it's a free access. That's</p> <p>13 something I don't know. So I cannot comment on</p> <p>14 it.</p> <p>15 I don't know what the number of samples</p> <p>16 is submitted. I don't know how it's curated. So</p> <p>17 therefore, when you look at a single site without</p> <p>18 having another one to superimpose it, you're going</p> <p>19 to have to ask the question: Is it reliable? As</p> <p>20 a scientist, I want reliability.</p> <p>21 (Exhibit No. 45 was marked for</p> <p>22 identification.)</p> <p>23 BY MR. PADGETT:</p> <p>24 Q Did -- I'm going to hand you what's been</p> <p>25 marked as Exhibit No. 45.</p>

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1 A Can I -- can I get rid of this?

2 Q Yes.

3 I believe you reference this in your

4 report on like page 41 or so. You state that:

5 "Mian suggests that acetaminophen intake during

6 pregnancy may increase both mother and fetal

7 exposure to NAPQI with levels at the highest in

8 the first trimester and dropping to 8.2 percent in

9 the third trimester."

10 Do you recall that part of your report?

11 A Yeah. That's what Mian had proposed in

12 his model.

13 Q Mian 2020 was not an experimental study

14 on animals or humans involving experimental

15 observations, right?

16 A It is a physiological based

17 pharmacokinetic modeling. So what they do is they

18 take actual human data and they model it, and

19 that's how they arrive at the model.

20 Q And it's a theoretical computer model,

21 right?

22 A It's so theoretical that the FDA accepts

23 it as data in the population. So therefore, you

24 could call it theoretical, but it is so important

25 that every major pharmaceutical company has a

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1 person that does this.

2 Q You're not talking about Mian

3 specifically there. You're talking about this

4 computer model?

5 A I'm -- the way -- what we call the term

6 PKPD -- PK -- sorry, PDP -- PBPK modeling is used

7 by almost all pharmacologists to the point that

8 the FDA has guidance as to how to use them.

9 Q What studies can you identify that

10 indicate there would be not enough GSH present in

11 the fetal brain to conjugate NAPQI that may be

12 present in the fetal brain?

13 A I think in my rebuttal report I use

14 Rigobello. It shows you that at 35 milligram per

15 kilogram, which is below the doses of hepatotoxic,

16 and in the offsprings, they develop -- they

17 actually analyze the brain, and they have

18 behavioral as well as movement differences. And

19 associated with GSH reduction in the brain.

20 MR. PADGETT: I'm sorry, what number are

21 we on now?

22 THE REPORTER: 46.

23 (Exhibit No. 46 was marked for

24 identification.)

25 BY MR. PADGETT:

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1 Q Dr. Louie, I'm going to hand you what's

2 been marked as Exhibit 46. Is that the Rigobello

3 report that you're talking about -- study article?

4 A It looks like it.

5 Q And what is it about Rigobello that you

6 say supports that there would be enough G- --

7 there would not be enough GSH present in the fetus

8 to conjugate NAP -- any NAPQI that may be in the

9 fetal brain?

10 Strike that.

11 What about Rigobello supports the

12 position there would be not enough GSH present in

13 the fetal brain to conjugate any NAPQI that may be

14 present in the fetal brain?

15 A So there are several things. One, look

16 at the concentration of what they call advanced

17 oxidation protein products, reduced glutathione,

18 in the level of lipid hydroperoxides and the

19 activity of superoxides were estimated in the

20 prefrontal, hippocampus, striatum, and the -- the

21 cerebellum of 22-day-old rats. These are the pups

22 or the offsprings.

23 And they show that these animals had

24 itself -- they had behavioral evaluation, and it

25 looks like there is some statistical differences

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1 between that and the control.

2 Q Is there any specific GSH finding in the

3 Rigobello study article?

4 A Sure. Look at Table 2, column PAR 35.

5 Okay. Look at GSH level. Look at the male in

6 control. It's 52.08. Compare that to the slide

7 over to the right, and you see here it --

8 paracetamol 35 milligram per kilogram, it drops it

9 down to 32.6. And it's bold, which suggests to

10 you that it is statistically significant.

11 Q And -- this is Table 2?

12 A Table 2, page 6. Go down to HPC, first

13 one is AOPP, the second one is GSH, and you see

14 that there.

15 Q Yes. And you're -- what you're saying

16 is that at 35 milligrams per kilogram of

17 acetaminophen, the males were -- had lower GC --

18 GSH.

19 A Okay.

20 Q Is that what you're saying?

21 A That's what I'm saying, in that location

22 of the brain.

23 You scroll down further, the superoxide

24 dismutase, go down to ST, and you see that SOD,

25 which is the last one, and then go to the right --

<p style="text-align: right;">Page 258</p> <p>1 one, two, three -- four, and notice there the 2 superoxide dismutase goes down. It's 3.6 versus 3 11.7. That tells you oxidative stress is way up. 4 Q Okay. And then for the 350 milligrams 5 per kilogram, there is no effect. In fact -- 6 A No, it's not statistically significant, 7 but if you look at the SOD at the 350, it's 5.97 8 versus 11.72. That's a twofold drop. 9 Q Would you agree that these results are 10 contrary to a dose-response in this study? 11 MR. ADAMS: Object to form. 12 THE WITNESS: I don't know if I agree to 13 that, but it's -- it in itself shows you that low 14 dose can cause this. 15 So to be fair, it's not just one point, 16 but it's two points. GSH and superoxide dismutase 17 are in the same antioxidant capacity. 18 So at the low hepatotoxic doses in the 19 pups -- remember the pups, not the mother -- 20 they're lower. So the mother's got it. So this 21 is telling you that they may or may not have 22 acetaminophen in their blood, but yet they have 23 brain issues. This is the consequences. 24 BY MR. PADGETT: 25 Q I believe you also reference in your</p>	<p style="text-align: right;">Page 260</p> <p>1 A Should have used a quantitative LC-MS. 2 It's 2020. It's no longer -- you can't use 3 something since 1969. 4 Q I'm going to turn back to Mian. 5 A Mian? 6 Q Mian. 7 A Okay. Oh, shoot, what did I do with it? 8 MR. ADAMS: Exhibit 45. 9 THE WITNESS: I have it. I don't know 10 where, but let's see -- yeah, I got it. Yes, I'm 11 there. 12 BY MR. PADGETT: 13 Q Okay. Sorry. Can -- instead, I want to 14 go to page 42 of your -- your report. Apologies. 15 A So can I put Mian away? 16 Q Yes. 17 A Thank you. 42 of my original report? 18 Q Yes. 19 There you state -- paragraph 108, you 20 state that: "The impact that acetaminophen intake 21 will have on GSH levels systemically in 22 site-specific tissue affects the potential adverse 23 events that may arise as a consequence of 24 acetaminophen exposure." 25 Do you see that?</p>
<p style="text-align: right;">Page 259</p> <p>1 report the Klein 2020 study. Were these GSH 2 findings replicated in the Klein 2020 study? 3 A Where -- where are you identifying this? 4 Klein? Or is it Koehn? 5 Q Klein 2020. 6 A 2020. 7 (Exhibit No. 47 was marked for 8 identification.) 9 BY MR. PADGETT: 10 Q I'm going to hand you what's been marked 11 as Exhibit 47, which is the Klein 2020 study. 12 Were the results of Rigobello on GSH 13 levels the same in Klein 2020 as in Rigobello 14 2021? 15 A I have never read this. 16 Q Was the Rigobello finding of GSH 17 replicated in Klein 2020? 18 A No. Because Klein used a colorimetric 19 assay, and a colorimetric assay is not definitive. 20 It's -- in fact, I know, I've used this 21 colorimetric assay. Not a good assay. Not good 22 at all. In fact, it's being rejected now. 23 Q So it's your testimony that Klein 2020 24 did not use a good assay as part of its 25 experimental protocol?</p>	<p style="text-align: right;">Page 261</p> <p>1 A Where do you see this? 2 Q Paragraph 108. 3 A I am seeing that, but -- what line are 4 you? 5 Q It's the sentence that starts "Thus." 6 A Okay, yes. 7 Q What studies are you relying on for that 8 statement? 9 A So this is actually sort of like 10 background. I didn't use -- I didn't use a -- any 11 paper, but it's well known that acetaminophen, the 12 higher the doses, the longer you take it, 13 glutathione will be reduced. 14 Q And by "site-specific tissue," do you 15 mean, for example, GSH levels in the brain as 16 opposed to other areas like the lung or the liver? 17 A It's in that context, yes. 18 Q Okay. And the site-specific issue here 19 is the fetal brain tissue, right? 20 A If you want it that way, yes. 21 Q I mean, if you disagree -- 22 A No, I'm just saying each -- as you and I 23 have gone back and forth, that the brain has 24 different levels than the liver, and then we 25 looked at different levels of -- in other tissues.</p>

<p style="text-align: right;">Page 262</p> <p>1 So, yeah, if you want to talk about the</p> <p>2 fetal, yeah.</p> <p>3 Q And then you state that study -- at the</p> <p>4 end of paragraph 109: "Studies have found both</p> <p>5 acute and chronic adverse outcomes in offspring of</p> <p>6 mothers associated with inadequate maternal GA --</p> <p>7 GSH and oxidative" stretch -- do you -- "stress."</p> <p>8 Do you see that?</p> <p>9 A You're talking about the last sentence?</p> <p>10 Q Yes.</p> <p>11 A Yeah.</p> <p>12 Q And after that, basically pages 42 to</p> <p>13 50, you talk about the Küster study 2011.</p> <p>14 A Mm-hmm.</p> <p>15 Q -- the Miranda Guisado study 2012, and</p> <p>16 the Vaziri study 2011, right?</p> <p>17 A Yeah.</p> <p>18 Q Okay. Küster involved very low birth</p> <p>19 weight prenatal babies with -- and it has no</p> <p>20 mention of acetaminophen, correct?</p> <p>21 A No. In fact, this section is talking</p> <p>22 about the impact of reduction in GSH levels have</p> <p>23 on the fetus.</p> <p>24 Q My question is, Küster does not involve</p> <p>25 acetaminophen, right?</p>	<p style="text-align: right;">Page 264</p> <p>1 Is it the disease that caused it or is it the low</p> <p>2 GSH that caused it?</p> <p>3 Q And I think -- and you -- some of the</p> <p>4 plaintiffs' experts in this case have pointed to</p> <p>5 oxidative stress levels in individuals with ADHD</p> <p>6 or ASD in children or adults, right? Have you</p> <p>7 seen those discussions?</p> <p>8 A Yes.</p> <p>9 Q Is the same true there, that it may be a</p> <p>10 matter of the condition or the disease itself</p> <p>11 leading to the increased levels of oxidative</p> <p>12 stress as opposed to fetal low -- increased levels</p> <p>13 of oxidative stretch -- stress leading to these</p> <p>14 conditions?</p> <p>15 MR. ADAMS: Object to form.</p> <p>16 THE WITNESS: I don't know what the word</p> <p>17 "stealth" means. So can you tell me what that</p> <p>18 means?</p> <p>19 BY MR. PADGETT:</p> <p>20 Q Which one?</p> <p>21 A Stealth. You used the word "stealth."</p> <p>22 Q Yeah, I wasn't trying to use that word.</p> <p>23 My question is --</p> <p>24 THE WITNESS: Can we reread back the --</p> <p>25 yeah, because I -- I'm like, what does that mean?</p>
<p style="text-align: right;">Page 263</p> <p>1 A Not in this study.</p> <p>2 Q Okay. It involves very low birth weight</p> <p>3 babies, right?</p> <p>4 A It talks about the impact of low GSH in</p> <p>5 relationship to low birth weight babies.</p> <p>6 Q Are you saying that low GSH leads to low</p> <p>7 birth weight, or are you -- is your point here</p> <p>8 that low birth weight leads to low GSH?</p> <p>9 A This section actually talks about the</p> <p>10 glutathione levels in relationship to -- to</p> <p>11 comorbidities found in -- in babies. So is it the</p> <p>12 low birth weight that causes that or is it the</p> <p>13 other way around? It doesn't -- these papers do</p> <p>14 not describe that.</p> <p>15 Q Okay. Do you have an opinion on that?</p> <p>16 MR. ADAMS: Object to form.</p> <p>17 THE WITNESS: I don't -- that's not my</p> <p>18 assignment.</p> <p>19 BY MR. PADGETT:</p> <p>20 Q Okay. But as you said, in this section</p> <p>21 you're talking about risk effects. None of these</p> <p>22 studies indicate that the low GSH is a causative</p> <p>23 factor for hypertension, preeclampsia, very low</p> <p>24 birth weight.</p> <p>25 A That's the -- a level of controversy.</p>	<p style="text-align: right;">Page 265</p> <p>1 BY MR. PADGETT:</p> <p>2 Q A number -- a number of studies have</p> <p>3 talked about increased oxidative stress in, for</p> <p>4 example, children and adults diagnosed with ASD or</p> <p>5 ADHD, right?</p> <p>6 A Yes. There are people who talked about</p> <p>7 a relationship between increased oxidative stress</p> <p>8 in relationship to the disease, yes.</p> <p>9 Q Okay. And my question is, oxidative</p> <p>10 stress levels, biomarkers for oxidative stress</p> <p>11 taken years after birth in somebody with ASD or</p> <p>12 ADHD, would you agree that that may be a part of</p> <p>13 the condition of having ASD or ADHD?</p> <p>14 MR. ADAMS: Object to form.</p> <p>15 BY MR. PADGETT:</p> <p>16 Q As opposed to an etiology from having</p> <p>17 higher oxidative stress while a fetus.</p> <p>18 MR. ADAMS: Object to form.</p> <p>19 THE WITNESS: So, I disagree with you</p> <p>20 for two reasons. First, you say it takes time for</p> <p>21 oxidative stress to occur. It's not true. You</p> <p>22 can have -- if I stuck a needle in you, you could</p> <p>23 have oxidative stress immediately. Stick two</p> <p>24 needles in you, it will be even faster. So it's</p> <p>25 acute as well as chronic.</p>

<p style="text-align: right;">Page 266</p> <p>1 Second, you're asking the question: Is</p> <p>2 it the cause or is it a symptom of the cause? I</p> <p>3 would tell you evidence suggests that it is the</p> <p>4 cause.</p> <p>5 BY MR. PADGETT:</p> <p>6 Q What evidence?</p> <p>7 A The evidence that you have depleted GSH,</p> <p>8 you have these issues. And I think I have it in</p> <p>9 my report as well.</p> <p>10 Q In fetal brain?</p> <p>11 A Your -- I'm giving you the answer as you</p> <p>12 start to narrow it. But I show you in -- I</p> <p>13 believe in one of the studies that they use BSO --</p> <p>14 that means they got rid of glutathione -- and they</p> <p>15 had diseases.</p> <p>16 So this is how people are using it,</p> <p>17 and -- and when they gave NAC back, the disease</p> <p>18 went away. So therefore, the data is suggesting</p> <p>19 that the oxidative stress is causing the issues.</p> <p>20 Causing the tissue damage.</p> <p>21 Q In the fetal brain?</p> <p>22 A It could. It's potentially quite</p> <p>23 possible.</p> <p>24 Q Okay. Would you agree in your -- I'm</p> <p>25 going back to your point if I gave you a shot or I</p>	<p style="text-align: right;">Page 268</p> <p>1 hypertension and, as you mentioned, it used BSO,</p> <p>2 not acetaminophen, right?</p> <p>3 A Yeah, it used BSO as a way to deplete</p> <p>4 glutathione.</p> <p>5 Q Okay. And again, it wasn't</p> <p>6 acetaminophen, correct?</p> <p>7 A It's a proof of principle that if you</p> <p>8 reduce glutathione, GSH, that you can induce</p> <p>9 diseases.</p> <p>10 Q Dr. Louie, my question is, did Vaziri</p> <p>11 2000 involve acetaminophen?</p> <p>12 MR. ADAMS: Object to form.</p> <p>13 THE WITNESS: I got to go back and look</p> <p>14 at the paper, but I'm pretty sure it doesn't.</p> <p>15 MR. PADGETT: Okay. Want to take a</p> <p>16 break?</p> <p>17 THE VIDEOGRAPHER: Going off the video</p> <p>18 record at 6:30 p.m. -- 5:44 p.m.</p> <p>19 (Recess.)</p> <p>20 THE VIDEOGRAPHER: We're going back on</p> <p>21 the video record at 6:03 p.m.</p> <p>22 BY MR. PADGETT:</p> <p>23 Q Dr. Louie, in paragraph 148 of your</p> <p>24 report you discuss the Koehn 2020 study.</p> <p>25 A Page 148 or paragraph 148?</p>
<p style="text-align: right;">Page 267</p> <p>1 gave you two, are you saying that that would cause</p> <p>2 stress in me?</p> <p>3 A That's what -- that's what the example</p> <p>4 means.</p> <p>5 Q Okay. And would -- and you're saying</p> <p>6 that stress results in oxidative stress. Is that</p> <p>7 correct?</p> <p>8 A That could be the case.</p> <p>9 Q Okay. Is your understanding that having</p> <p>10 ASD can cause stress in a child or an adult human?</p> <p>11 A It could, but it could be the other way</p> <p>12 around, oxidative stress is causing the kid to</p> <p>13 have those issues.</p> <p>14 Q And these biomarker oxidative stress</p> <p>15 studies, though, are -- they're looking at levels</p> <p>16 years after birth, right?</p> <p>17 A In -- that's -- that's in children that</p> <p>18 were born and have those issues.</p> <p>19 And so people are now asking if you</p> <p>20 reduce the oxidative stress, can you reduce ASD</p> <p>21 and ADHD. That's why people are testing</p> <p>22 glutathione as well as NAC in a clinical trial.</p> <p>23 Q Have you heard of autism burnout?</p> <p>24 A No.</p> <p>25 Q Okay. The Vaziri study involved</p>	<p style="text-align: right;">Page 269</p> <p>1 Q Paragraph 148. Apologies.</p> <p>2 (Exhibit No. 48 was marked for</p> <p>3 identification.)</p> <p>4 BY MR. PADGETT:</p> <p>5 Q And there you reference the -- as I</p> <p>6 said, the Koehn 2020 study. I'm going to hand you</p> <p>7 what's been marked as Exhibit 48.</p> <p>8 Is that the Koehn 2020 study that you're</p> <p>9 referencing there in paragraph 1 --</p> <p>10 A I don't remember it being this thick. I</p> <p>11 guess -- because I get it in a typed PDF. Can I</p> <p>12 take a look at it?</p> <p>13 Q Yes.</p> <p>14 A (Peruses document.)</p> <p>15 It looks like it. It's just in a very</p> <p>16 different format.</p> <p>17 Q You mentioned a different format. Have</p> <p>18 you -- are you familiar with the F1000Research</p> <p>19 platform where this study was published?</p> <p>20 A What do you mean "familiar"? Can you be</p> <p>21 more specific?</p> <p>22 Q Have you heard of this -- this online</p> <p>23 publication journal F1000Research?</p> <p>24 A Have I heard of it?</p> <p>25 Q Yes.</p>

<p style="text-align: right;">Page 270</p> <p>1 A Obviously if I referred to it, I've read</p> <p>2 it, right.</p> <p>3 Q Well, I'm talking about the -- the</p> <p>4 journal, so to speak, F1000Research.</p> <p>5 A It's a -- it's an okay journal.</p> <p>6 Q Okay journal?</p> <p>7 Have -- have you ever published an</p> <p>8 article in a journal or online platform like this</p> <p>9 where peer review happens after the article is</p> <p>10 published?</p> <p>11 A I think that's occurring more and more</p> <p>12 now.</p> <p>13 Q Have you ever done that?</p> <p>14 A No. I normally go to very high -- high</p> <p>15 impact journals.</p> <p>16 Q Okay. And F1000Research is not a high</p> <p>17 impact journal?</p> <p>18 A I'm a snob.</p> <p>19 Q Okay.</p> <p>20 A Just -- just because I need it to be</p> <p>21 high impact journals that get grants.</p> <p>22 Q So my question is, is F1000Research a</p> <p>23 high impact journal?</p> <p>24 A It's average, as I said.</p> <p>25 Q Okay. The Koehn study administered</p>	<p style="text-align: right;">Page 272</p> <p>1 A Paragraph 178.</p> <p>2 Q Yes.</p> <p>3 A But -- you mean 148 or 178? I want to</p> <p>4 make sure, because 178 is almost at the end.</p> <p>5 Q Okay. 148. Look at 148.</p> <p>6 A Oh, you mean the rat treated acutely or</p> <p>7 chronically with acetaminophen were compared to</p> <p>8 untreated?</p> <p>9 Q Right.</p> <p>10 A Okay.</p> <p>11 Q My question to you is, what do you mean</p> <p>12 by untreated rats there?</p> <p>13 A Not treated.</p> <p>14 Q Okay. Did the untreated rats in Koehn</p> <p>15 receive a vehicle IP injection?</p> <p>16 A I don't think so, but let me check just</p> <p>17 to make sure, because I wouldn't write "untreated"</p> <p>18 if there's a vehicle.</p> <p>19 (Peruses document.) I don't see a</p> <p>20 vehicle here.</p> <p>21 Q Okay. So the controls were just left</p> <p>22 alone and didn't get any type of IP injection with</p> <p>23 vehicle. Right?</p> <p>24 A Yeah, they -- I don't know if they were</p> <p>25 left alone. They could be handled and then put</p>
<p style="text-align: right;">Page 271</p> <p>1 acetaminophen via intraperitoneal injection in</p> <p>2 pregnant rats. Right?</p> <p>3 A Yes.</p> <p>4 Q Twice daily and embryonic day E15 to 19,</p> <p>5 and as a single dose at E19, right?</p> <p>6 A That's what it says there.</p> <p>7 Q Okay. We already talked about whether</p> <p>8 IP injection is stressful and bypasses first pass</p> <p>9 metabolism.</p> <p>10 Will you agree that drug metabolite</p> <p>11 concentrations achieved in a maternal animal via</p> <p>12 IP injection would be different than those that</p> <p>13 would occur via oral administration?</p> <p>14 A I would disagree with you.</p> <p>15 Q Why?</p> <p>16 A It depends on the time that you sample.</p> <p>17 IP has an earlier peak, but oral would have a</p> <p>18 longer absorption time.</p> <p>19 Q You state that the treated group was --</p> <p>20 in your report, I think it's 178 -- you state that</p> <p>21 the treated group was compared to untreated rats,</p> <p>22 right?</p> <p>23 A I want to make sure -- let's see. Where</p> <p>24 are you reading this from? I'm sorry.</p> <p>25 Q It's paragraph 178 of your report.</p>	<p style="text-align: right;">Page 273</p> <p>1 back, yeah.</p> <p>2 Q But they didn't get treated with IP</p> <p>3 injection vehicle.</p> <p>4 A That could be -- yeah, that's how I</p> <p>5 would interpret it.</p> <p>6 Q Okay. You -- we discussed IP injection</p> <p>7 is stressful for rats. Agreed?</p> <p>8 A I think I told you they can tolerate it</p> <p>9 and it's not a problem.</p> <p>10 Q But would you agree that the untreated</p> <p>11 rats were not receiving IP injections like the</p> <p>12 treated rats were?</p> <p>13 A Yeah, we could say that. Yeah, we could</p> <p>14 say that.</p> <p>15 Q This was twice a day on several days,</p> <p>16 the treated rats were getting the IP injections</p> <p>17 and the untreated rats got nothing.</p> <p>18 A I get your point that -- that twice a</p> <p>19 day is a stress.</p> <p>20 Q As you pointed to me, that that would</p> <p>21 stress me out if you gave me a shot twice a day,</p> <p>22 right, or two shots?</p> <p>23 A Right, but I'm just -- just reminding</p> <p>24 you that rats, at least in my lab, get it for 60</p> <p>25 days.</p>

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1 Q Is it your opinion that it's
2 scientifically proper for a study design to use
3 controls that don't receive vehicle IP injection
4 when the treated animals are getting IP injections
5 twice a day?
6 A That -- that would be -- yeah, it says
7 here "untreated rats." Yeah.
8 Say what? I'm sorry.
9 Q Is it your opinion that it's
10 scientifically proper for a study design to use
11 controls that don't receive a vehicle IP injection
12 when the treated rats for several days are getting
13 IP injections twice a day?
14 MR. ADAMS: Object to form.
15 THE WITNESS: Yeah. So the injection
16 is -- is sodium chloride or saline. I would think
17 that it's not -- it's not that -- it's well
18 tolerated.
19 BY MR. PADGETT:
20 Q Have you ever done a study involving IP
21 injections?
22 A Of course.
23 Q Okay. When you do IP injection studies
24 comparing controls to treated rodents, do you have
25 controls treated with vehicle via IP injection?

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1 A We do.
2 Q Okay. And again, I think you
3 answered -- you said it's tolerated, but in your
4 opinion, is it scientifically proper for a study
5 design to use controls that don't receive a
6 vehicle IP injection when the treated animals for
7 several days are getting IP injections twice a
8 day?
9 MR. ADAMS: Object to form.
10 MR. PADGETT: He still hasn't answered.
11 THE WITNESS: Repeat that once more so I
12 can answer you correctly.
13 BY MR. PADGETT:
14 Q Is it scientifically -- you already
15 testified that you give IP injections of vehicle
16 to the control animals, right?
17 But is it your opinion that it's
18 scientifically still proper for a study design to
19 use controls that don't receive vehicle IP
20 injections when the treated rats for several days
21 are getting two IP injections?
22 MR. ADAMS: Object to form.
23 THE WITNESS: Yeah, so this is what
24 scientists say is a study -- it's not a fatal
25 flaw. It's a flaw.

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1 BY MR. PADGETT:
2 Q Okay.
3 A But it's not a fatal flaw. It's a flaw
4 that has to be addressed. Yeah, I mean, you --
5 that's the consideration that you have to look at.
6 Q Okay. If you look at page 4 of Koehn --
7 A Page 4 of Koehn.
8 Q -- where it says "Animals."
9 A Yeah.
10 Q It's the paragraph right after the
11 "Animals" section.
12 A You mean drugs and markers, or are you
13 looking at --
14 Q Above that, that paragraph above,
15 "Animals."
16 A The "Animals" section. Okay.
17 Q Yes.
18 And there the authors state -- it's kind
19 of in the middle of the paragraph starting the
20 sentence "Animal numbers" -- "Animal numbers were
21 based on a previous experience of such experiments
22 and were the minimum number required to detect a
23 significant difference."
24 Do you see that? Between groups at P --
25 A Okay. And --

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1 Q -- less than .05.
2 A I see. Yes.
3 Q Is it your opinion that's a
4 scientifically appropriate method for determining
5 sufficient sample size?
6 MR. ADAMS: Object to form.
7 THE WITNESS: Actually, that would be a
8 very proper -- that's the correct way of doing it.
9 If you know that -- so you know, most
10 animal research -- research centers limits our
11 number of animals, and they will tell you do a
12 power analysis that is only statistical -- that
13 will allow you to get your statistical
14 significance. Not too many more, because PETA
15 will come and hunt us down.
16 BY MR. PADGETT:
17 Q Do you see on page 7 under "Results,"
18 the N number is 4. Do you see that?
19 A N -- where are you looking at?
20 Q Page 7.
21 A Page 7.
22 Q There's a bunch of colored circles, and
23 right above that on the right column is "Results."
24 A I see that.
25 Q Untreated controls, the N was 4. Do you

<p style="text-align: right;">Page 278</p> <p>1 see that?</p> <p>2 A Mm-hmm. Yes, I do. Sorry.</p> <p>3 Q Do you think that's a proper sample</p> <p>4 size?</p> <p>5 A If you want to do a T test, three is all</p> <p>6 you need.</p> <p>7 Q This result that was based on reviewing</p> <p>8 one placenta and one fetus per dam, right?</p> <p>9 A I -- I'm sorry. I'm not following what</p> <p>10 you just said.</p> <p>11 Q The "Results" section is based on</p> <p>12 reviewing one placenta and one fetus per dam?</p> <p>13 A Per dam.</p> <p>14 Q Right.</p> <p>15 A Okay. And I believe that this is a</p> <p>16 transcriptomics data. Do you agree with that?</p> <p>17 Figure 1 is a transcriptomics data. Do you know</p> <p>18 what that is?</p> <p>19 Q My question is, was it one fetus per dam</p> <p>20 for placenta --</p> <p>21 A So in transcriptomics you don't need big</p> <p>22 numbers. This is, as you showed me in the other</p> <p>23 paper, and of one for the fetus, this is something</p> <p>24 that you got to be careful about how you overly</p> <p>25 interpret the data. But, yeah, this is</p>	<p style="text-align: right;">Page 280</p> <p>1 that's N of 1. Look at Figure 4. And you look at</p> <p>2 here, it's N of 4 for each, and it talks about</p> <p>3 transcripts.</p> <p>4 So I want to make sure that we're</p> <p>5 talking the same way. I think each dot represents</p> <p>6 an animal or a treatment. So that's why I didn't</p> <p>7 understand what you meant that N of 1.</p> <p>8 Q Can you turn to page 33. Page -- I want</p> <p>9 to talk about pages 33 and 34 of this exhibit.</p> <p>10 It's the Koehn 2020 article.</p> <p>11 A 33?</p> <p>12 Q This is the post-publication reviewers</p> <p>13 and replies from the authors.</p> <p>14 A Hmm.</p> <p>15 Q If you look at the bottom of page 33 --</p> <p>16 A Mm-hmm.</p> <p>17 Q -- one of the reviewers commented that,</p> <p>18 quote: It is a pity that the number of dams is</p> <p>19 too small to assess the significance of this</p> <p>20 observation, and that no housekeeping protein was</p> <p>21 used to normalize AFP expression.</p> <p>22 Do you see that?</p> <p>23 A I do see that.</p> <p>24 Q Okay. And then can you turn to the next</p> <p>25 page.</p>
<p style="text-align: right;">Page 279</p> <p>1 transcriptomics data, if I remember correctly.</p> <p>2 Q But it's based on reviewing one placenta</p> <p>3 and one fetus per dam, right?</p> <p>4 A Where do you see that?</p> <p>5 Q You don't know what -- the answer?</p> <p>6 MR. ADAMS: Object to form.</p> <p>7 THE WITNESS: I asked you where do you</p> <p>8 see that?</p> <p>9 BY MR. PADGETT:</p> <p>10 Q I recalled it from reading the study,</p> <p>11 but do you know whether that is true?</p> <p>12 A I don't recollect, but I will -- there's</p> <p>13 no N here, so it's kind of hard to figure out.</p> <p>14 Q Okay. You also note in your report when</p> <p>15 you're discussing Koehn: "The fetal and maternal</p> <p>16 plasma and cerebral spinal fluid were measured for</p> <p>17 AFP and IL-1B."</p> <p>18 Is that the interleukin you were talking</p> <p>19 about earlier?</p> <p>20 A The interleukin-1 beta.</p> <p>21 Q Okay. Given that the AFP data is based</p> <p>22 on a number of one or two per group, would you</p> <p>23 agree that the differences could be due to</p> <p>24 individual variability?</p> <p>25 A So, Counsel, I think I disagree with you</p>	<p style="text-align: right;">Page 281</p> <p>1 And the authors agree that: "It is a</p> <p>2 pity that the numbers were very small, but we were</p> <p>3 constrained by the effects of being shut out of</p> <p>4 our laboratories for several months because of the</p> <p>5 Coronavirus emergency."</p> <p>6 Do you see that?</p> <p>7 A Yeah. So let me go back to your last</p> <p>8 sentence that you said there was no beta-actin.</p> <p>9 There was not N of 1. There's one, two, three,</p> <p>10 four again. And they did it in duplicates.</p> <p>11 So, yes, a beta-actin would have been</p> <p>12 helpful, but it's very consistent between the dams</p> <p>13 AFP versus across all of them.</p> <p>14 Q Did the --</p> <p>15 A Oh, I know this guy.</p> <p>16 Q Which guy?</p> <p>17 A The author.</p> <p>18 Q Okay.</p> <p>19 A I went to high school with him.</p> <p>20 Q Do -- if you go to Figure 5 of the</p> <p>21 report.</p> <p>22 A Figure 5 of the report.</p> <p>23 Q There's a lot of figures.</p> <p>24 And you mentioned the interleukin B</p> <p>25 concentration. Do the authors actually indicate</p>

<p style="text-align: right;">Page 282</p> <p>1 that there was a statistically significant change</p> <p>2 in the interleukin B levels with acetaminophen</p> <p>3 exposure in the fetuses?</p> <p>4 A So they don't say any statistical</p> <p>5 analysis here, but you start to see the bars are</p> <p>6 starting to go up. So, yes, there's some low and</p> <p>7 there's some high.</p> <p>8 And so you have to ask the question, how</p> <p>9 many of them are low, which are on the dotted</p> <p>10 line, and you count the number of dots above it.</p> <p>11 That sort of gives you the idea that the chronic</p> <p>12 actually had more numbers. So this sort of gives</p> <p>13 you the idea that, hmm, that -- that they had</p> <p>14 bigger numbers.</p> <p>15 Q But they weren't able to identify it,</p> <p>16 which one reviewer said was a pity and the author</p> <p>17 agreed, as to whether it was statistically</p> <p>18 significant. Right?</p> <p>19 A Fair enough.</p> <p>20 Q Okay. And if you can turn to the front</p> <p>21 page in the abstract -- first, I want to ask, you</p> <p>22 state in paragraph 150 of your report -- if you</p> <p>23 could turn to that.</p> <p>24 A Paragraph 150.</p> <p>25 Q Yeah. You're talking about Koehn still.</p>	<p style="text-align: right;">Page 284</p> <p>1 saying here at the end of the abstract?</p> <p>2 A No. Because if you look at your</p> <p>3 Figure 5, do you see the dams that have any high</p> <p>4 levels? Go to number 5. There's no elevation.</p> <p>5 Whereas you start to use the chronic ones, you see</p> <p>6 the dots start to go up.</p> <p>7 So this is in page 20 of 37, Figure 5.</p> <p>8 Q But the authors say the gene regulatory</p> <p>9 changes were less prominent in the fetal brain</p> <p>10 than in the placenta of treated fetuses --</p> <p>11 A Well --</p> <p>12 Q -- and did not involve the inflammatory-</p> <p>13 related genes.</p> <p>14 A But in this data that they show, they</p> <p>15 show this in protein level, not transcripts. Just</p> <p>16 because someone writes something doesn't mean</p> <p>17 they're always right.</p> <p>18 Q Okay.</p> <p>19 A They have to look at their own data. I</p> <p>20 mean, their own data shows that there is -- that</p> <p>21 the IL-1 in the fetus was much -- is higher than</p> <p>22 that of dams.</p> <p>23 Q I know you went to high school with one</p> <p>24 of the authors, but you weren't there doing the</p> <p>25 study, right?</p>
<p style="text-align: right;">Page 283</p> <p>1 These findings suggest -- quote: These findings</p> <p>2 suggest that acetaminophen treatment during</p> <p>3 pregnancy can induce inflammatory response and</p> <p>4 potentially affect the fetus but not the mother,</p> <p>5 end quote.</p> <p>6 Do you see that?</p> <p>7 A I did say that.</p> <p>8 Q Okay. At the end of the abstract, the</p> <p>9 authors state, quote: In the fetal brain, gene</p> <p>10 regulatory changes were less prominent in the</p> <p>11 placenta of treated fetuses and did not involve</p> <p>12 inflammatory-related genes; there was no evidence</p> <p>13 of increased blood-brain barrier permeability.</p> <p>14 A Can you show me where you --</p> <p>15 Q The last sentence of the abstract.</p> <p>16 A The abstract. (Peruses document.)</p> <p>17 It did state that, but it also tells you</p> <p>18 that there is -- it's less prominent, which means</p> <p>19 it occurs, and it tells you that the placenta was</p> <p>20 highly affected.</p> <p>21 Q But you say in paragraph 50 that the</p> <p>22 findings suggest that inflammatory -- induced</p> <p>23 inflammatory response can potentially affect the</p> <p>24 fetus but not the mother.</p> <p>25 Isn't that the opposite of what they're</p>	<p style="text-align: right;">Page 285</p> <p>1 A Oh, no, no. Oh, in fact -- in fact, the</p> <p>2 guy -- not the author. The reviewer.</p> <p>3 Q The reviewer. Oh, okay.</p> <p>4 A Yeah.</p> <p>5 Q Are you saying they misinterpreted their</p> <p>6 own study or their own data in this study?</p> <p>7 MR. ADAMS: Object to form.</p> <p>8 THE WITNESS: I'm just saying that they</p> <p>9 could have been better at what they -- how they</p> <p>10 handled it.</p> <p>11 And in fact, in Figure 4, it shows you</p> <p>12 statistical significance in the placenta, in the</p> <p>13 chronic instead of the acute.</p> <p>14 (Exhibit No. 49 was marked for</p> <p>15 identification.)</p> <p>16 BY MR. PADGETT:</p> <p>17 Q I'm going to hand you what's been marked</p> <p>18 as Exhibit 49, Doctor, Nuttall 2003.</p> <p>19 And do you agree that Exhibit 49 is a</p> <p>20 Nuttall 2003 study article?</p> <p>21 A It is.</p> <p>22 Q Okay. And this study measured serum</p> <p>23 acetaminophen concentration and total antioxidant</p> <p>24 capacity in fifteen 19- to 32-year-olds taking</p> <p>25 acetaminophen 14 days straight. Right?</p>

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1 A That's what the method says.

2 Q Okay. They're not assessing

3 acetaminophen -- serum acetaminophen concentration

4 and total antioxidant capacity in an embryo or a

5 fetus from the mother's use of acetaminophen,

6 right?

7 A They are not, but they tell you if it's

8 the same age women who is pregnant, that they

9 would have similar effects. That's -- this is a

10 clinical evaluation looking at the impact,

11 assuming that a woman pregnant at the same age

12 will have the same effects.

13 Q You're assuming that.

14 A Not assuming it. That's how we develop

15 drugs. That -- you can't -- if that's the case,

16 I'd have to draw blood on every patient who gets a

17 drug.

18 Q And --

19 A So therefore, to ascertain what you just

20 said, and the FDA says, I'm good with you if only

21 it's 35 patients or even 15 patients. There's no

22 disconnect. Same age, male or female, drug levels

23 are therapeutic, so therefore you see the PK.

24 This is why we use the term

25 "pharmacokinetic, pharmacodynamic," and they show

Page 287

1 the pharmacodynamic effects.

2 Q It's not looking at the levels of the

3 fetal brain, right?

4 A Then again you always narrow down, but

5 if it's in the blood, you're reducing the total

6 antioxidant activity, you're using glutathione,

7 which then at that point makes the baby

8 susceptible to what? Makes them susceptible to

9 comorbidities.

10 Q What do you mean by comorbidities?

11 A So we talked about, the glutathione

12 reduction in very low birth weight kids. A lot of

13 your -- your ASD patients have low birth weight,

14 and ADHD patients have low birth weight. So

15 therefore, there is a correlation.

16 Q In Nuttall -- I'm looking at page 290 in

17 the right column.

18 A 290.

19 Q The study methods indicate that blood

20 samples were taken hourly for a period of four

21 hours after swallowing 1 gram of acetaminophen,

22 correct?

23 A Two tablets of 500 milligrams, yes.

24 Q And the blood samples were taken hourly

25 every four hours after taking that 1 gram of

Page 288

1 acetaminophen, right?

2 A That's what this sampling strategy is.

3 Q And do you know how the sampling was

4 done with these subjects?

5 A I'm not sure what you just asked.

6 Q How was -- was -- was the blood samples

7 taken by blood draw?

8 A Normally that's how it's done.

9 Q Okay. This study does not indicate

10 whether there was a control group, right?

11 A You don't need a control group. Because

12 in this -- oh, it's a venipuncture. That means

13 from the blood. Venous blood was taken. So they

14 don't need the control group.

15 Q Well, you indicated earlier that if you

16 gave me a shot and then a second shot, it would

17 cause stress. Right?

18 A Mm-hmm.

19 Q And stress can cause oxidative stress,

20 right?

21 A Mm-hmm.

22 Q Okay. And would you agree that drawing

23 blood via puncture, as you put it, four times a

24 day would cause stress to individuals included in

25 this study?

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1 A Oh, you're mistaking how we draw blood.

2 We put a catheter in there. We don't draw your

3 blood four times. We just pull it out from the

4 same catheter. There's no -- there is no

5 morbidity associated with that.

6 Q Is that -- that's how it was done here?

7 A They said venipuncture.

8 Q Okay.

9 A So there's no -- number one, there is no

10 stress. It is done all the time for every drug

11 that we put through the FDA. So this -- this is

12 not a stressful thing.

13 Q The authors found a 10 percent reduction

14 of antioxidant capacity. You indicate that on

15 page 51 of your report.

16 If you look at Figure 5, that result is

17 based on one hour following ingestion of 1 gram,

18 the highest single dose of acetaminophen, right?

19 A There is no highest dose. It's only one

20 dose, 1 gram four times a day.

21 Q One gram is the maximum dose -- single

22 dose per acetaminophen product labels, right?

23 A That's therapeutic dose.

24 Q It's the maximum dose, right?

25 MR. ADAMS: Object to form.

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1 THE WITNESS: Yes.

2 BY MR. PADGETT:

3 Q And there's a 10 percent reduction based

4 on taking the samples one hour after ingestion,

5 right?

6 A You look at -- Figure 5, you're looking

7 at one hour?

8 Q Yes.

9 A There is no one hour in Figure 5.

10 There's a 4-hour, 6 -- 5 hours, 10-hour, 14-hour.

11 Q It says: "Serum total antioxidant

12 capacity determined by 10 percent recovery of

13 original signal as an indicator of the presence of

14 strong antioxidants within a sample, one hour

15 following ingestion of 1 gram paracetamol."

16 Do you see that?

17 A Oh, I see what you're talking about.

18 Oh, those are days. My apologies. You're

19 correct.

20 Q Okay. And this was followed the same

21 throughout the study, right?

22 A No. Figure 4 tells you that they did it

23 hourly over four hours, and they actually looked

24 at it.

25 MR. ADAMS: Counsel, one of the ways I

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1 protect my client from the grilling is the seven

2 hours are up.

3 MR. PADGETT: Okay. Note -- are we at

4 seven hours?

5 THE VIDEOGRAPHER: 7:02.

6 MR. PADGETT: Okay. Can I take two

7 minutes, three minutes to finish this line of

8 questioning?

9 MR. ADAMS: Whenever somebody says two

10 to three, it usually turns out to five and ten.

11 What do I do?

12 MR. PADGETT: How about two --

13 MR. ADAMS: Two questions.

14 MR. PADGETT: How about two questions?

15 MR. ADAMS: Two questions, that's fair,

16 yes.

17 BY MR. PADGETT:

18 Q Is a 10 percent decline a depletion in

19 your opinion of antioxidant capacity?

20 A You see the stars on these studies?

21 It's -- these are antioxidant, which includes a

22 lot of glutathione and vitamin E and vitamin A and

23 vitamin D. This is a lot of drug.

24 Q You didn't answer my question. Is it a

25 depletion of antioxidant capacity, a 10 percent

Page 292

1 drop?

2 A Is it a depletion? So your body remakes

3 it. On day 14, it's way down. It is going down.

4 How much more if you go 28 days? I don't know the

5 answer.

6 Q Does the Nuttall study indicate clinical

7 hepatotoxicity is occurring in the liver?

8 A Nuttall doesn't do that, but Jetton did

9 show that.

10 MR. PADGETT: Thank you for your time,

11 Dr. Louie.

12 THE WITNESS: Thank you.

13 MR. ADAMS: Take a short break off the

14 record.

15 THE VIDEOGRAPHER: We're going off the

16 video record at 6:38 p.m.

17 (Recess.)

18 THE VIDEOGRAPHER: We are going back on

19 the video record at 6:47 p.m.

20 EXAMINATION

21 BY MR. ADAMS:

22 Q Dr. Louie, good afternoon.

23 Can you put in front of you your amended

24 report, Exhibit 21.

25 A Yes.

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1 Q I want you to turn to page 9.

2 Are you there?

3 A Yes, I am.

4 Q Paragraph 31, you write: "I hold the

5 foregoing opinions to a reasonable degree of

6 scientific certainty."

7 Do you see that?

8 A I do.

9 Q What do you mean by "a reasonable degree

10 of scientific certainty"?

11 A It's more likely to occur than not.

12 Q Now, when we -- turn to -- let's see --

13 page 22 of your report.

14 A Let me get to it.

15 Q Yep. You've got in your heading at

16 number 4, just above paragraph 66, you write:

17 "Analysis of lines of evidence that support the

18 causal association between prenatal acetaminophen

19 exposure and ASD/ADHD in outcomes."

20 Do you see that?

21 A I do.

22 Q And then you also use the phrase "causal

23 association" in subheading A. Do you see that?

24 A I do.

25 Q When you -- when you used the phrase

<p style="text-align: right;">Page 294</p> <p>1 "causal association," what do you mean?</p> <p>2 A It's likely to occur. It is going to --</p> <p>3 it's going to cause it.</p> <p>4 Q And by the "it," what are we talking</p> <p>5 about here?</p> <p>6 A That if you give acetaminophen to a</p> <p>7 pregnant women for 28 days, it is likely to occur.</p> <p>8 Q Now, and the "it" that is likely to</p> <p>9 occur, specifically in this case, what is the "it"</p> <p>10 that you think will occur if you give the amount</p> <p>11 of the therapeutic dose for the duration of time</p> <p>12 that you looked at?</p> <p>13 A It's going to increase the risk of</p> <p>14 getting ASD or ADHD.</p> <p>15 Q And that opinion is that that risk is</p> <p>16 increased by?</p> <p>17 A Twofold.</p> <p>18 Q Now, let's turn to page -- paragraph 17</p> <p>19 of your report.</p> <p>20 A Paragraph 17?</p> <p>21 Q Yeah. Before I ask you any questions</p> <p>22 about that, now, you were asked to do a --</p> <p>23 something in this case, right, and you identify it</p> <p>24 in paragraph 15?</p> <p>25 A In paragraph 15.</p>	<p style="text-align: right;">Page 296</p> <p>1 use a methodology or approach that you made up</p> <p>2 specifically for this case, or did you use one</p> <p>3 that -- that you've been using standard for your</p> <p>4 career?</p> <p>5 MR. PADGETT: Object to form.</p> <p>6 THE WITNESS: What I did in forming my</p> <p>7 opinion and my search, I do what's standard, and</p> <p>8 that standard is called -- we actually have a</p> <p>9 class on that. It's called "Medical Literature</p> <p>10 Evaluation." So all pharmacists, pharmacologists,</p> <p>11 and even graduate students now are -- you know,</p> <p>12 are taught how to do this.</p> <p>13 BY MR. ADAMS:</p> <p>14 Q And that -- I point you to paragraph 17</p> <p>15 of your report. You mention in your report at</p> <p>16 paragraph 17 a "Medical Literature Evaluation,</p> <p>17 MLE." Do you see that?</p> <p>18 A I do.</p> <p>19 Q Can you describe for us generally what</p> <p>20 that is?</p> <p>21 A Well, it's a course that teaches you how</p> <p>22 to address a -- a scientific question. It could</p> <p>23 be pharmacology based. It could be just a disease</p> <p>24 base. So it's agnostic to that.</p> <p>25 What it does is that it -- when there's</p>
<p style="text-align: right;">Page 295</p> <p>1 Q Yep.</p> <p>2 A Yes.</p> <p>3 Q The assignment that was given to you, is</p> <p>4 that something that clinical pharmacologists like</p> <p>5 yourself are trained to do?</p> <p>6 A I am, and most clinical pharmacologists</p> <p>7 are able to do this.</p> <p>8 Q Now, what you've been assigned to do in</p> <p>9 this case is to look at the publicly available</p> <p>10 evidence to determine the duration and dose or</p> <p>11 duration at which prenatal exposure to</p> <p>12 acetaminophen increases the risk of developing</p> <p>13 autism spectrum disorder and ADHD, true?</p> <p>14 MR. PADGETT: Objection. Leading.</p> <p>15 Object to form.</p> <p>16 BY MR. ADAMS:</p> <p>17 Q Right?</p> <p>18 A That's what it says.</p> <p>19 Q And did you do that in this case?</p> <p>20 A I did.</p> <p>21 Q Now, when you -- when you did that, did</p> <p>22 you use an approach or a methodology that you made</p> <p>23 up, or did you use one that -- withdrawn. Let me</p> <p>24 ask a better question.</p> <p>25 When you did your assignment, did you</p>	<p style="text-align: right;">Page 297</p> <p>1 a question, you need to formulate the question.</p> <p>2 And when you formulate the question, you should be</p> <p>3 able to have search terms.</p> <p>4 So therefore, what we do is normally get</p> <p>5 the major search terms, put it in PubMed, which is</p> <p>6 a national library of -- I guess of medicine. And</p> <p>7 so what we do is, at that point it will generate a</p> <p>8 list of papers, and from these papers, we could</p> <p>9 refine them. What we do is we review the papers,</p> <p>10 look at the abstracts, and see if we can refine</p> <p>11 the subject matter.</p> <p>12 Q Let me point you to paragraph 18 of your</p> <p>13 report. At the -- in the last sentence at the</p> <p>14 bottom, there's two lines on the bottom, I see the</p> <p>15 word "PICO methodology" there.</p> <p>16 A Yes, I see that.</p> <p>17 MR. PADGETT: Object to form.</p> <p>18 BY MR. ADAMS:</p> <p>19 Q What is a PICO methodology?</p> <p>20 A So it stands for -- PICO is -- is</p> <p>21 abbreviation for populate -- the P stands for</p> <p>22 population, patient or even problem. The I stands</p> <p>23 for intervention. And the intervention could be</p> <p>24 not just the drug or the intervention but the dose</p> <p>25 and the -- the -- and the frequency you give that.</p>

<p style="text-align: right;">Page 298</p> <p>1 C stands for comparison, control. So therefore,</p> <p>2 is -- are the studies well controlled? Are the</p> <p>3 studies -- do they have -- is it -- is it</p> <p>4 stratified?</p> <p>5 Q Is this -- is this methodology a</p> <p>6 methodology that is -- that is unique to --</p> <p>7 withdrawn.</p> <p>8 Is it a methodology that is used</p> <p>9 standard in your field or not?</p> <p>10 A Well, we teach it. Number one, we teach</p> <p>11 it to every student, every pharmacy student gets</p> <p>12 it. And our PhD students, they learn it, but they</p> <p>13 don't learn it just by class. They learn it by we</p> <p>14 take a paper, we break it apart for them, and so</p> <p>15 how valid is the paper, what are the limitations.</p> <p>16 Q In doing your MLE methodology in this</p> <p>17 case, did you utilize the PICO methodology in any</p> <p>18 way?</p> <p>19 A I did.</p> <p>20 Q And how do you use the PICO methodology?</p> <p>21 A So I think I say in my -- in my report</p> <p>22 that I put in the -- the three major search terms:</p> <p>23 "Acetaminophen," which is the drug, "pregnancy,"</p> <p>24 and then what I did was I put "autism spectrum</p> <p>25 disorder" or "autism." I -- all of those minutia</p>	<p style="text-align: right;">Page 300</p> <p>1 Everybody has a different -- they call it</p> <p>2 differently for the course, but the course is</p> <p>3 essentially looking at biostatistics, looking at</p> <p>4 how to use databases. It includes how to develop</p> <p>5 the question. How do you know that you're right?</p> <p>6 And is there -- is there more than one level of</p> <p>7 evidence? Do you -- and what we try to teach the</p> <p>8 students is that if there's more than one level of</p> <p>9 evidence, do you develop confidence in your</p> <p>10 decision-making?</p> <p>11 Q Without looking at the book or a book,</p> <p>12 based on your experience, Dr. Louie, would you be</p> <p>13 able to just generally walk us through the steps</p> <p>14 of the MLE that you use in your field and that you</p> <p>15 used in this case?</p> <p>16 A I -- I think I can. It's -- I do this</p> <p>17 almost every day because I read papers every day.</p> <p>18 One of the first things is, what</p> <p>19 journal was it published in? Right. Is it a good</p> <p>20 journal? Is there a -- and so you can tell that</p> <p>21 by something called impact factor. And impact</p> <p>22 factor of 1 is -- is -- I believe it's average.</p> <p>23 Impact of greater than 10 is considered</p> <p>24 outstanding. So therefore -- and don't look at</p> <p>25 the levels like 1, 2, 3, 4, it gets better. There</p>
<p style="text-align: right;">Page 299</p> <p>1 we use. And then take that out and put "ADHD"</p> <p>2 versus the entire word. So therefore, I try to</p> <p>3 cast as wide a net as I can.</p> <p>4 Q In using the PICO methodology, is that</p> <p>5 something that is common or uncommon in your field</p> <p>6 when you're trying to come up with the answer to</p> <p>7 the question that -- that you were asked to come</p> <p>8 up with in this case?</p> <p>9 MR. PADGETT: Object to form.</p> <p>10 THE WITNESS: We use it. We don't -- we</p> <p>11 may not talk, you know, like this is the PICO</p> <p>12 method, but it's -- it is how we train all our</p> <p>13 students. And the reason we train all our</p> <p>14 students, because there's a discipline called drug</p> <p>15 information where a lot of our students go to drug</p> <p>16 companies and answer questions for clinicians.</p> <p>17 BY MR. ADAMS:</p> <p>18 Q This MLE methodology, is that something</p> <p>19 that if someone wanted to try to figure out what</p> <p>20 it is, what -- if it has steps, if it actually</p> <p>21 exists, would you be able to find that anywhere?</p> <p>22 Is it published anywhere?</p> <p>23 A There's books that -- that we use. I</p> <p>24 think we have chapters in books as how to -- we</p> <p>25 call it how to address clinical questions.</p>	<p style="text-align: right;">Page 301</p> <p>1 is quantum leaps above 10.</p> <p>2 Q Let's take a look at paragraph 65 of</p> <p>3 your report.</p> <p>4 A Paragraph 65?</p> <p>5 Q Yeah. Now -- are you there? It's on</p> <p>6 page 21.</p> <p>7 A Yeah. Yes.</p> <p>8 Q One of the things you write in there</p> <p>9 about one of the -- I guess the studies is this</p> <p>10 2021 Consensus Statement as published in the</p> <p>11 Nature Reviews Endocrinology, and then you write</p> <p>12 it's a well-respected and rigorously peer-reviewed</p> <p>13 journal.</p> <p>14 Do you see that?</p> <p>15 A I see that.</p> <p>16 Q Is that -- is that something that you</p> <p>17 factor into when you're -- when you're evaluating</p> <p>18 studies to come up with the answer that you would</p> <p>19 give in this case?</p> <p>20 MR. PADGETT: Object to form.</p> <p>21 THE WITNESS: That is a standard thing I</p> <p>22 look at. I look at the paper. If it's from the</p> <p>23 New England Journal of Medicine versus Nature,</p> <p>24 which are considered the most outstanding impact</p> <p>25 factors, compared to something called</p>

<p style="text-align: right;">Page 302</p> <p>1 Pharmacotherapy, which is -- has a good impact</p> <p>2 factor of 4, 3 to 4.</p> <p>3 But I'm going to look at the higher</p> <p>4 impact journals because they have been rigorously</p> <p>5 reviewed by the peer reviewers themselves. And so</p> <p>6 sort of give you the idea that where it's</p> <p>7 published tells you who's looking at it and how</p> <p>8 hard they look at it.</p> <p>9 BY MR. ADAMS:</p> <p>10 Q As part of your evaluation as to the --</p> <p>11 what studies are useful or not, do you take into</p> <p>12 consideration the -- the study design?</p> <p>13 A Oh, absolutely. There's two things that</p> <p>14 you always look at, right. And I might have</p> <p>15 missed this. Not only where is it published, who</p> <p>16 are the authors. So are the authors known to be</p> <p>17 people who are leaders in the field.</p> <p>18 And I also look at if the papers -- who</p> <p>19 funds them, because you -- if it's, let's say, a</p> <p>20 drug company funding the paper, there may be some</p> <p>21 conflicts, there may be some bias. And -- but if</p> <p>22 it's supported by the NIH or using all these big</p> <p>23 grants, and some of these studies were supported</p> <p>24 by the NIH. In fact, I think most of them were</p> <p>25 supported by the NIH.</p>	<p style="text-align: right;">Page 304</p> <p>1 Q And then you look at paragraph 74,</p> <p>2 and you say regarding the Ystrom: "The findings</p> <p>3 by Brandlistuen et al. were supported by Ystrom</p> <p>4 et al., and which I also gave weight to because of</p> <p>5 its strong study design."</p> <p>6 Do you see that?</p> <p>7 MR. PADGETT: Object to form.</p> <p>8 THE WITNESS: I do see that.</p> <p>9 BY MR. ADAMS:</p> <p>10 Q Can you tell us whether or not this is</p> <p>11 an example of you using this study design factor</p> <p>12 or is it telling us something else?</p> <p>13 A Well, if you look at my paragraph 74 --</p> <p>14 one, two, three, four -- line 4, I said "this</p> <p>15 cohort." I always highlight -- give an overview</p> <p>16 of what the study design looked like. It says</p> <p>17 involved 112,000, over 120 -- 112,000 offsprings</p> <p>18 with children -- with 2,246 children diagnosed</p> <p>19 with ADHD.</p> <p>20 So I always ask the question, is this --</p> <p>21 is the number -- the frequency, is it what I</p> <p>22 expect or is it higher than what I expect? And if</p> <p>23 it's higher than I expect, what makes it go up?</p> <p>24 So therefore, I can understand what the -- the</p> <p>25 control and the noise may be.</p>
<p style="text-align: right;">Page 303</p> <p>1 Q In doing your MLE methodology, let's</p> <p>2 focus on the study design, did you -- did you</p> <p>3 consider that factor in doing your -- your</p> <p>4 evaluation?</p> <p>5 A I always do. I always look at several</p> <p>6 things. What's the number? Do they have a</p> <p>7 control group? What is the control group? Right,</p> <p>8 what is the control group? And how long did</p> <p>9 they -- did they look over this? How big -- not</p> <p>10 only how big is the cohort, when was the cohort</p> <p>11 developed? And has there been a change in the way</p> <p>12 we -- we treat patients?</p> <p>13 Is there different technology? Like,</p> <p>14 for example, in the olden days we use HPLC. Now</p> <p>15 we use LC-MS or liquid chromatography-mass</p> <p>16 spectrometry, which is a lot more precise and a lot</p> <p>17 more sensitive.</p> <p>18 Q If you turn to paragraph 71 of your</p> <p>19 report.</p> <p>20 A Mm-hmm.</p> <p>21 Q The first sentence you write: "I assign</p> <p>22 the greatest weight to Brandlistuen 2013 because</p> <p>23 it employed the strongest study design."</p> <p>24 Do you see that?</p> <p>25 A I do.</p>	<p style="text-align: right;">Page 305</p> <p>1 Q I'm not going to go over all the</p> <p>2 factors. I just want to focus on one last factor</p> <p>3 in this -- the MLE methodology.</p> <p>4 Is one of the factors in this</p> <p>5 methodology that you would look to how other</p> <p>6 authors interpret the same studies, and then see</p> <p>7 whether or not they're consistent with your</p> <p>8 interpretation?</p> <p>9 MR. PADGETT: Object to form.</p> <p>10 THE WITNESS: Normally when I read a</p> <p>11 paper, I always tell my students and myself to be</p> <p>12 agnostic on what the conclusions were. I not only</p> <p>13 look at the abstract, I look at the methods and I</p> <p>14 look at the data.</p> <p>15 And there's a reason why I do that.</p> <p>16 Does the data match the abstract? And does -- are</p> <p>17 the authors overinterpreting or underinterpreting?</p> <p>18 There are -- I have actually found papers that</p> <p>19 underinterpret, and to my advantage, I published</p> <p>20 on them. And so therefore, they didn't look at</p> <p>21 that. I did the same study, and this time I</p> <p>22 looked at it, and I got it published.</p> <p>23 BY MR. ADAMS:</p> <p>24 Q Is the MLE methodology a reliable or an</p> <p>25 unreliable way to come up with the answer to the</p>

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1 question that you were asked in this case?

2 MR. PADGETT: Object to form.

3 THE WITNESS: Well, it's -- it's the

4 standard. If that's the standard -- and this is

5 what we teach all of our students -- you know,

6 it's -- it would be very hard to say that it's --

7 it's an invalid method because this is what we've

8 been teaching our students, easily when I was a

9 student, and it's about 35 years now -- don't

10 laugh -- but we still teach it, and it is still a

11 fundamental course in our curriculum. In fact, I

12 think it's a required course.

13 BY MR. ADAMS:

14 Q I want you to pull in front of you

15 Exhibits 27 and 28.

16 A 27, 28. Can you tell me the paper?

17 Q Yes, they're the Liew papers. So 27 --

18 I'm sorry, I should have done this -- 27 is -- 28

19 is Liew 2016, and 27, I think it has a --

20 A It's the Liew paper.

21 Q Yeah, it's the other Liew paper. I

22 don't have the date on it. 2014.

23 A I'm sorry, I have so many papers. Oh,

24 you have it? Can I --

25 Q Well, I have my copies.

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1 A The Liew -- what year?

2 Q So let's start with the 2016, so that

3 will be Exhibit 28.

4 A I probably lost my copy. Somewhere --

5 it's here somewhere. My apologies.

6 I don't have it in here. I've got Liew

7 2014. Can we start with that?

8 Q Let's start with 2016, 28.

9 A It's empty.

10 MR. ADAMS: Ben, can you see if you can

11 find that for him over there?

12 THE WITNESS: Oh, I know where it is.

13 It's back there.

14 BY MR. ADAMS:

15 Q Watch your microphone.

16 A This is Liew, right? This one, 27, yes.

17 Let me get my mic back. Sorry.

18 MR. PADGETT: 28 is 2016.

19 THE WITNESS: No, it's Exhibit 27.

20 BY MR. ADAMS:

21 Q No, we're going to start with

22 Exhibit 28. I have this as the 2016.

23 A Okay. And -- okay, I got that. This

24 one.

25 Q Yes.

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1 A Okay.

2 Q Counsel asked you some questions about

3 this study, specifically about whether or not this

4 study adjusted for familial and genetic

5 confounding.

6 Do you remember that?

7 A Yes.

8 Q I want you to take a look at page 953 of

9 the study.

10 A Okay, 953.

11 Q Yes. And I want you to look at the

12 paragraph -- it's the first full paragraph on the

13 left side that starts "All models were adjusted."

14 A I see it.

15 Q I want you to read that paragraph, and

16 then after you read that paragraph, tell us

17 whether or not that sheds any light at all as to

18 whether or not this study confounded for any

19 familial and genetic confounding.

20 A Yes, it did. It talked about

21 self-reported maternal psychiatric illness.

22 Mothers were asked if they had seen a doctor or a

23 psychologist because of depression, anxiety,

24 childhood psychiatric disorders or other mental

25 health problems.

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1 Q Does it shed any light as to whether or

2 not this study --

3 A Yeah, it does.

4 Q -- adjusted?

5 A It does. It was adjusted, according

6 to -- to this paper.

7 Q Now, one of the things you testified to

8 earlier was that in your own research you used

9 Tylenol to induce hepatotoxicity in mice.

10 Do you recall that testimony?

11 A Hepatotoxicity in mice, yes.

12 Q And you testified 150 milligrams per

13 kilogram is not always hepatotoxic -- hepatotoxic,

14 right?

15 MR. PADGETT: Object to form.

16 THE WITNESS: That's what I said.

17 BY MR. ADAMS:

18 Q Can you clarify what you meant by that?

19 A Even though you give 150 milligram per

20 kilogram in a mice, not all of them develop

21 hepatotoxicity signs or histological.

22 Q Could something cause liver function but

23 still be considered within the range of an

24 equivalent human therapeutic dose?

25 MR. PADGETT: Object to form.

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1 THE WITNESS: I think I mentioned that
 2 in my report, as well as in my testimony here,
 3 that Jetton et al. used below 1 gram given four
 4 times a day, had signals of hepatotoxicity.
 5 That's normal dose. Or normal therapeutic dose.
 6 Yes, that can occur.
 7 MR. ADAMS: I have no further questions
 8 at this time.
 9 MR. PADGETT: You don't have any
 10 additional exhibit -- I thought you said you --
 11 you don't have an additional exhibit?
 12 MR. ADAMS: I'm not sure I understand
 13 the question.
 14 MR. PADGETT: Never mind.
 15 How long was that?
 16 THE VIDEOGRAPHER: 25 minutes.
 17 MR. PADGETT: We can take a short break.
 18 We get an equal --
 19 MR. ADAMS: Go off the record.
 20 MR. PADGETT: We can switch places.
 21 THE VIDEOGRAPHER: We're going off the
 22 video record at 7:13 p.m.
 23 (Recess.)
 24 THE VIDEOGRAPHER: We are going back on
 25 the video record at 7:30 p.m.

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1 FURTHER EXAMINATION
 2 BY MR. PADGETT:
 3 Q Dr. Louie, just a few follow-up
 4 questions about some things that doctor -- or that
 5 Mr. Adams discussed with you.
 6 You were talking about your -- your MLE
 7 methodology, and you were talking about the search
 8 terms that were used to find the studies that you
 9 reviewed, and those search terms that you were
 10 using included "acetaminophen," "ASD" or autism,
 11 "ADHD," attention-deficit/hyperactivity disorder,
 12 and then you did kind of a special search for
 13 glutathione issues, right?
 14 A No, I said -- it's in my report that
 15 says, "acetaminophen," "pregnancy," "ASD." Then I
 16 take the ASD out, and then "ADHD."
 17 Q What about the -- you mentioned there
 18 was a separate search on glutathione.
 19 A I did that separately, yes.
 20 Q Okay. And was that part of your -- your
 21 MLE methodology?
 22 A Using the same methodology.
 23 Q Okay. And we discussed Exhibit 43, if
 24 you want to look at it, was the Raijmakers --
 25 A Okay.

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1 Q -- study. I believe it's Raijmakers
 2 is --
 3 MR. ADAMS: I have to object to being
 4 beyond the scope of what I asked. Can we -- can
 5 you promise me that this is within the scope?
 6 MR. PADGETT: It's -- this is totally
 7 within the scope of your M- -- of your MLE
 8 questioning.
 9 MR. ADAMS: All right.
 10 BY MR. PADGETT:
 11 Q Raijmakers study 2001, right?
 12 A Exhibit 43.
 13 Q Yes.
 14 A Mm-hmm.
 15 Q That's the Raijmakers, and that is about
 16 glutathione in embryonic and early fetal tissues,
 17 right?
 18 A That's correct, which looks like only
 19 one sample per time point.
 20 Q Okay. That study was not on your
 21 materials -- list of materials, and it was not a
 22 study that you reviewed before issuing either one
 23 of -- any of your reports in this case, right?
 24 A I don't remember seeing it.
 25 Q Okay. And I think it was Exhibit 31,

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1 the Bandoli study.
 2 A 31.
 3 Q It is the Bandoli 2019 study.
 4 Somebody likes their Huey Lewis.
 5 Exhibit 31.
 6 A I'm down to 35, 33 -- oh, shoot, I don't
 7 have it. Where is it?
 8 Do you have an extra copy?
 9 Q It's Exhibit 31.
 10 A I don't have it here. 29, 24.
 11 MR. PADGETT: Can we go off the record?
 12 MR. ADAMS: What are we looking for?
 13 MR. PADGETT: Exhibit 31, the Bandoli
 14 study.
 15 THE WITNESS: I can't find it.
 16 THE VIDEOGRAPHER: Going off the record.
 17 One moment.
 18 MR. PADGETT: Do you have a copy of
 19 that, Julien?
 20 THE VIDEOGRAPHER: We're going off the
 21 video record at 7:35.
 22 THE WITNESS: Okay, thank you.
 23 (Pause in the proceedings.)
 24 THE VIDEOGRAPHER: Go back on. We are
 25 going back on the video record at 7:35 p.m.

<p style="text-align: right;">Page 314</p> <p>1 BY MR. PADGETT:</p> <p>2 Q Okay. And you were saying that</p> <p>3 pregnancy, acetaminophen, that should have been --</p> <p>4 studies relating to those two search terms should</p> <p>5 have been included in your MLE methodology and</p> <p>6 your search terms. Agree?</p> <p>7 A No, I don't agree.</p> <p>8 Q Okay. Your search terms pursuant to</p> <p>9 your MLE methodology included "acetaminophen" and</p> <p>10 "pregnancy," correct?</p> <p>11 A And those AS -- "ASD" or "ADHD."</p> <p>12 Q And so they had to include "ASD" or</p> <p>13 "ADHD"?</p> <p>14 A That's what the terms were. That's what</p> <p>15 I was asked to address.</p> <p>16 Q Okay. And there were -- you did not as</p> <p>17 a part of your methodology look for studies on</p> <p>18 acetaminophen and pregnancy related to use -- the</p> <p>19 frequency of use and comorbidity factors for ASD</p> <p>20 or ADHD.</p> <p>21 MR. ADAMS: Object to form.</p> <p>22 BY MR. PADGETT:</p> <p>23 Q Did your search terms include that?</p> <p>24 MR. ADAMS: Object to form.</p> <p>25 THE WITNESS: I think I -- I stated in</p>	<p style="text-align: right;">Page 316</p> <p>1 as a part of your search?</p> <p>2 MR. ADAMS: Object to form.</p> <p>3 THE WITNESS: So, Counsel, I did it not</p> <p>4 only with the PubMed, I also did a Google search,</p> <p>5 and neither of them came up with this paper.</p> <p>6 BY MR. PADGETT:</p> <p>7 Q Okay. And if you look at reference 12</p> <p>8 of Bandoli, it says: "Association" -- and this is</p> <p>9 the Hoover study -- "association between prenatal</p> <p>10 acetaminophen exposure and future risk of</p> <p>11 attention-deficit/hyperactivity disorder in</p> <p>12 children." Right?</p> <p>13 A I see it.</p> <p>14 Q Okay. Your search terms should have</p> <p>15 picked up the Bandoli study, which is about the</p> <p>16 frequency of acetaminophen use and characteristics</p> <p>17 of risk factors that have been, as you testified,</p> <p>18 associated with ASD or ADHD, right?</p> <p>19 MR. ADAMS: Object to form.</p> <p>20 THE WITNESS: Counsel, it didn't show</p> <p>21 up. And so you keep telling -- I don't run -- I</p> <p>22 have no idea how -- how these computers work. I</p> <p>23 never -- and if it doesn't come out, I wouldn't</p> <p>24 know.</p> <p>25 And if I did look at this, I'm trying to</p>
<p style="text-align: right;">Page 315</p> <p>1 my report how I did it.</p> <p>2 BY MR. PADGETT:</p> <p>3 Q Okay.</p> <p>4 A And the number of hits. And I don't</p> <p>5 recollect this because this does not talk about</p> <p>6 ASD or ADHD. Or am I missing it?</p> <p>7 Q This was part of the mother to baby, the</p> <p>8 MoBa cohort, right?</p> <p>9 A I don't know that.</p> <p>10 This is not the MoBa. Definitely not.</p> <p>11 Q Oh, the mother to baby study?</p> <p>12 A They're not the same.</p> <p>13 Q Okay. So your methodology did not</p> <p>14 involve an examination of looking at acetaminophen</p> <p>15 use and frequency of use compared to risk factors</p> <p>16 for ASD or ADHD unless it contained the words</p> <p>17 AD -- "ADHD" or "ASD"?</p> <p>18 MR. ADAMS: Object to form.</p> <p>19 THE WITNESS: You're starting to add</p> <p>20 things, so it's really confusing. So if you could</p> <p>21 break down your questions, it would be helpful.</p> <p>22 BY MR. PADGETT:</p> <p>23 Q Well, why don't we -- why don't you --</p> <p>24 can you explain to me why the Bandoli study was</p> <p>25 not located or a part of your reference materials</p>	<p style="text-align: right;">Page 317</p> <p>1 understand how this even relates to ASD and ADHD</p> <p>2 because it just talks about other issues. So I</p> <p>3 would read it, but I don't know how to incorporate</p> <p>4 that.</p> <p>5 BY MR. PADGETT:</p> <p>6 Q Your MLE methodology, as Mr. Adams</p> <p>7 walked through with you, resulted in the opinions,</p> <p>8 according to your testimony, that are laid out in</p> <p>9 your report, right?</p> <p>10 A I used the search. I expanded the</p> <p>11 search. I looked at review articles. I looked at</p> <p>12 pertinent articles. But if this is the only paper</p> <p>13 I missed -- and like I said, "ASD" and "ADHD" is</p> <p>14 not in this paper. So there -- it makes sense, it</p> <p>15 didn't connect.</p> <p>16 Q Well, what do you -- it's referenced in</p> <p>17 reference 12 -- number 14, reference 14 is: "Use</p> <p>18 of acetaminophen during pregnancy and the risk of</p> <p>19 autism spectrum disorder in offspring."</p> <p>20 Do you see that?</p> <p>21 A Where are you talking about this?</p> <p>22 Q Reference 14 in the Bandoli study.</p> <p>23 A Mm-hmm.</p> <p>24 Q Do you see that? "Use of acetaminophen</p> <p>25 during pregnancy and the risk of autism spectrum</p>

<p style="text-align: right;">Page 318</p> <p>1 disorder in the offspring."</p> <p>2 Are you saying that your search terms</p> <p>3 didn't capture references in these studies that</p> <p>4 you were looking for?</p> <p>5 MR. ADAMS: Object to form.</p> <p>6 THE WITNESS: Is this number 14?</p> <p>7 BY MR. PADGETT:</p> <p>8 Q Yes.</p> <p>9 A It looks like a review article.</p> <p>10 Q But according --</p> <p>11 A Wait, wait, wait. I'm looking for --</p> <p>12 your -- a review article is -- is not a primary</p> <p>13 article. Your -- your expert witness gets mad</p> <p>14 that I use a review article, and yet they can use</p> <p>15 a review article.</p> <p>16 I'm just asking the question. I cover</p> <p>17 as many papers as I can. I was agnostic in what</p> <p>18 I'm doing. I did not do anything, and you're</p> <p>19 essentially saying that I did this -- sort of put</p> <p>20 me in a box that I -- I -- I cherry-picked this,</p> <p>21 as we would call it.</p> <p>22 Q Or did not cherry-pick this.</p> <p>23 A I'm offended. I want to say that to</p> <p>24 you. I never saw this. I was very -- very honest</p> <p>25 with you that when I didn't see a paper, I didn't</p>	<p style="text-align: right;">Page 320</p> <p>1 and pair it to the risk of autism or ADHD called</p> <p>2 Chen 2019? Do you recall seeing that study?</p> <p>3 A I don't have the paper in front of me,</p> <p>4 so I don't know.</p> <p>5 Q If it was not on your list -- your list</p> <p>6 of materials, would the studies that you located</p> <p>7 and found and relied on, were those included in</p> <p>8 your list of materials that came with your report?</p> <p>9 A It should be.</p> <p>10 Q I think it was Exhibit 47, Klein -- the</p> <p>11 Klein 2020 study.</p> <p>12 Let me know when you're able to locate</p> <p>13 it.</p> <p>14 A 47?</p> <p>15 Q Yeah, 47.</p> <p>16 I promise I'm not stealing any exhibits.</p> <p>17 A I'm sorry?</p> <p>18 Q I promise I'm not stealing any exhibits.</p> <p>19 THE WITNESS: Thank you.</p> <p>20 BY MR. PADGETT:</p> <p>21 Q Mr. Adams just put Klein 2020 before you</p> <p>22 now?</p> <p>23 A Yes.</p> <p>24 Q Okay. When we talked about Klein 2020,</p> <p>25 it didn't replicate findings of Rigobello, and</p>
<p style="text-align: right;">Page 319</p> <p>1 see it.</p> <p>2 But if there's that much data and it was</p> <p>3 so pertinent, tell me where does this show you</p> <p>4 that there's ASD/ADHD in this paper.</p> <p>5 Q I guess my question, Dr. Louie, is that</p> <p>6 is if acetamin- -- if acetaminophen and ASD and</p> <p>7 ADHD are contained in this paper, it should have</p> <p>8 popped up on your search terms as a part of your</p> <p>9 MLE protocol.</p> <p>10 A How do you know?</p> <p>11 MR. ADAMS: One second. Let him finish</p> <p>12 the question.</p> <p>13 Object to form.</p> <p>14 THE WITNESS: Can I answer?</p> <p>15 BY MR. PADGETT:</p> <p>16 Q Go ahead.</p> <p>17 A How do you know that that's how the -- I</p> <p>18 don't know how Medline works or PubMed works. If</p> <p>19 you do know, let me know.</p> <p>20 Q Did -- I think -- do you recall -- I</p> <p>21 don't -- I think I may have raised this.</p> <p>22 Do you recall reading a study that</p> <p>23 looked at insurance records of acetaminophen use</p> <p>24 for pregnant women to arrive at a cumulative dose</p> <p>25 and used that to calculate that cumulative dosing</p>	<p style="text-align: right;">Page 321</p> <p>1 your testimony -- and that was not on your list of</p> <p>2 materials, correct, Klein 2020?</p> <p>3 A No, it wasn't. But as I told you, there</p> <p>4 was a real problem with this paper because 2.33 is</p> <p>5 using a very bad assay.</p> <p>6 Q Okay. And --</p> <p>7 A I would have rejected it because of that</p> <p>8 even if I did find it.</p> <p>9 Q Okay. Could you turn to, and I hate to</p> <p>10 ask this, Exhibit 46, which is the Rigobello --</p> <p>11 A Yes.</p> <p>12 Q -- 2021 study.</p> <p>13 A 2021 -- yes, okay.</p> <p>14 Q What assay method did the Rigobello 2021</p> <p>15 study use?</p> <p>16 A They used the same.</p> <p>17 MR. PADGETT: Okay. That's all the</p> <p>18 questions I have. Thank you, Mr. Louie.</p> <p>19 THE WITNESS: Are we done?</p> <p>20 MR. ADAMS: Yes.</p> <p>21 THE VIDEOGRAPHER: Ready to conclude?</p> <p>22 Hold on, please.</p> <p>23 This concludes the video deposition of</p> <p>24 Dr. Stan G. Louie. Going off the record at</p> <p>25 7:48 p.m.</p>

Confidential Subject to Protective Order

<p style="text-align: right;">Page 322</p> <p>1 (Whereupon, the deposition of 2 STAN G. LOUIE, PharmD was concluded 3 at 7:48 p.m.) 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p>	<p style="text-align: right;">Page 324</p> <p>1 INSTRUCTIONS TO WITNESS 2 Please read your deposition over carefully and 3 make any necessary corrections. You should state 4 the reason in the appropriate space on the errata 5 sheet for any corrections that are made. 6 After doing so, please sign the errata sheet 7 and date it. 8 You are signing same subject to the changes 9 you have noted on the errata sheet, which will be 10 attached to your deposition. It is imperative 11 that you return the original errata sheet to the 12 deposing attorney within thirty (30) days of 13 receipt of the deposition transcript by you. If 14 you fail to do so, the deposition transcript may 15 be deemed to be accurate and may be used in court. 16 17 18 19 20 21 22 23 24 25</p>
<p style="text-align: right;">Page 323</p> <p>1 CERTIFICATE OF CERTIFIED SHORTHAND REPORTER 2 The undersigned Certified Shorthand Reporter 3 does hereby certify: 4 That the foregoing proceeding was taken before 5 me at the time therein set forth, at which time 6 the witness was duly sworn; That the testimony of 7 the witness and all objections made at the time of 8 the examination were recorded stenographically by 9 me and were thereafter transcribed, said 10 transcript being a true and correct copy of my 11 shorthand notes thereof; That the dismantling of 12 the original transcript will void the reporter's 13 certificate. 14 In witness thereof, I have subscribed my name 15 this date: August 7, 2023. 16 17 _____ 18 LESLIE A. TODD, CSR, RPR 19 Certificate No. 5129 20 21 (The foregoing certification of 22 this transcript does not apply to any 23 reproduction of the same by any means, 24 unless under the direct control and/or 25 supervision of the certifying reporter.)</p>	<p style="text-align: right;">Page 325</p> <p>1 ----- 2 E R R A T A 3 ----- 4 PAGE LINE CHANGE 5 _____ 6 REASON: _____ 7 _____ 8 REASON: _____ 9 _____ 10 REASON: _____ 11 _____ 12 REASON: _____ 13 _____ 14 REASON: _____ 15 _____ 16 REASON: _____ 17 _____ 18 REASON: _____ 19 _____ 20 REASON: _____ 21 _____ 22 REASON: _____ 23 _____ 24 REASON: _____ 25</p>

1 ACKNOWLEDGMENT OF DEPONENT
2 I, _____, do hereby
3 certify that I have read the foregoing pages, and
4 that the same is a correct transcription of the
5 answers given by me to the questions therein
6 propounded, except for the corrections or changes
7 in form or substance, if any, noted in the
8 attached Errata Sheet.

9

10 _____

11 STAN G. LOUIE, PharmD DATE

12

13

14 Subscribed and sworn to

15 before me this

16 ____ day of _____, 20____.

17 My commission expires: _____

18 _____

19 Notary Public

20

21

22

23

24

25

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